EXHIBIT A

THE UNIVERSITY OF CHICAGO
THE PRITZKER SCHOOL OF MEDICINE

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Re: Valsartan Litigation

Dear Counsel,

Please find a report regarding my opinions on this case below.

1. Biography/Qualifications

I am a physician, duly licensed to practice medicine in the State of Illinois. I have completed a Bachelor of Science in Biochemistry and a Doctor of Medicine, and then completed medical training in Internal Medicine residency and a Hematology & Oncology fellowship. I have also completed a Master of Science in Health Studies (Biostatistics, Clinical and Translational Investigation). I am Board Certified in Medical Oncology and practice clinically in the field of Medical Oncology with a subspecialty in Gastrointestinal Oncology, including treating patients with gastroesophageal, pancreatic, hepatobiliary (liver and bile duct), neuroendocrine, and small and large bowel cancers. I have been involved in these patients' care including various therapies in the perioperative curative-intent as well palliative metastatic settings. I conduct research in these same tumor types from both clinical and basic research perspectives.

At the University of Chicago, I am the Director of Gastrointestinal (GI) Medical Oncology Program. This entails overseeing a clinical program that includes 6 GI Medical Oncology Faculty members, 3 Advanced Nurse Practitioners, 6 nurse navigators, and a Pharmacist, as it pertains to operations of the clinical and research programs within GI Medical Oncology. Annually, we have a census of > 1600 GI cancer patients, of which >350 are new patient and new consultation visits. In addition, I oversee and run the research program that includes 4 clinical trial coordinators, 4 data managers, regulatory personnel, and biobank personnel. The GI research program has more than 30 investigational clinical trials open at the moment. This extends to 3 community satellite centers of the University of Chicago where our studies are available. As the Director of Interdisciplinary GI Oncology and Assistant Director of Translational Research, this research focus extends to the other oncologic disciplines of GI Surgical Oncology, Radiation Oncology, as well as Anatomical and Molecular Pathology, where I oversee and facilitate cross-discipline collaboration and research.

I have authored numerous publications focusing on the management of GI and other cancers, as well as biologic mechanisms of cancer growth, novel therapeutics, and mechanisms of therapeutic resistance of these diseases. I have presented these topics and my research findings internationally at medical conferences and by invitation to academic centers. I have obtained NIH/NCI research funding, foundation awards, collaboration with biotech and pharmaceutical companies, and philanthropy to support my work. A primary research focus of mine is on the biological understanding and treatment of gastroesophageal (esophagus, gastroesophageal junction, and stomach) cancers, by studying the normal and oncologic components and molecular pathways of gastrointestinal cells. My research agenda has an overarching goal to validate and improve personalized treatment, immunotherapy, and precision medicine for gastroesophageal cancer and other GI cancers, with findings often relevant to all cancers. A major component of my research is on the quantification of tumor genetic molecular heterogeneity both between individuals with gastroesophageal cancer, but importantly also within a given individual within one tumor site, and from one tumor site to another, and how this impacts personalized targeted therapeutic approaches. To overcome many biological hurdles of the disease that has led to failed therapeutic approaches in the past 1-2 decades, I have designed and executed novel clinical trials to implement treatment strategies based on these laboratory and clinical discoveries.

I serve as a mentor to medical trainees including medical students, internal medicine and surgical residents, as well as medical oncology and surgical oncology fellowship trainees. Most teaching is part of clinical training during clinical care of patients in the inpatient and outpatient setting. I also teach formal didactic lectures to these trainees on the topics of management of various GI cancers. I also teach didactic lectures to first and third year Graduate Students in Cancer Biology regarding the biologic underpinnings of GI cancer and therapeutic strategies.

I serve as associate editor for the Journal of American Medical Association Network Open (JAMA Netw Open), and I am also on the editorial boards of the Journal of Clinical Oncology Precision Oncology (J Clin Oncol PO), the journal Cancer, and the journal Cancers. As associate editor for the Oncology section of JAMA Netw Open, I review manuscript submissions pertaining to all cancers and from all disciplines (medical, surgical, and radiation oncology) to the journal and determine which manuscripts will be sent for external peer review versus those that would be rejected without review. I then review those manuscripts and external peer reviewer comments and provide a final decision as to whether to reject or accept the paper for publication. As associate editor of JAMA Netw Open and member of the editorial boards of J Clin Oncol PO, Cancer, and Cancers, I attend regular board meetings to discuss papers and general operations of the journals. I also serve as an ad hoc reviewer for numerous journals to serve as an external peer reviewer to provide comments and recommendations on acceptance of manuscripts, pertaining to GI cancers, submitted for publication.

I am a member of many medical societies and groups, including the American Society of Clinical Oncology (ASCO), European Society of Medical Oncology (ESMO), and the American Association of Cancer Research (AACR). I have participated in consensus guidelines for the treatment of GI cancers for ASCO and other Consortia.

A copy of my curriculum vitae is attached as Exhibit A.

2. Scope and Summary of Opinions

I have been asked to describe cancer in general terms, and the ways in which cancer develops in humans (cancer pathogenesis or carcinogenesis). More specifically, I have been asked to describe a) aerodigestive cancers, including gastrointestinal (GI) cancers (esophageal, gastric, pancreatic, liver and colorectal/intestinal cancers), lung and pharyngeal cancers, genitourinary (GU) cancers (bladder, kidney, prostate, and uterine cancers), breast cancers, and hematologic (blood) malignancies; b) known causes and risk factors that are associated with these cancers, their general carcinogenesis timeline, and their overall incidences annually; and c) surveillance strategies and rationale as it pertains to primary and secondary screening interventions for each of these cancers.

In addition, I have been asked to evaluate the question of whether there is reliable scientific evidence, including consideration of epidemiologic, toxicological, and animal data, that the antihypertensive valsartan containing drugs (VCDs) (or other angiotensin receptor II blockers (ARBs) like losartan, irbesartan, and others) and in particular VCDs identified to have trace levels of the impurities N-nitrosodimethylamine (NDMA) and/or N-Nitrosodiethylamine (NDEA), are associated with or cause cancer of any type. My report focuses on NDMA as this

is the area with the most available data regarding these questions, but my interpretation and conclusions of these data generally pertain to NDEA as well.

Methods/Materials Reviewed:

This report is offered pursuant to Rule 26 of the Federal Rules of Civil Procedure. Each of the opinions I have offered in this report is given to a reasonable degree of medical probability and/or certainty, and is based on the same methodology I routinely use in my professional life as an active cancer researcher and scientific journal editor, reviewer, and publisher. I reviewed and analyzed the available medical and scientific literature on these subjects, in particular, literature pertaining to the risk factors for cancer, background rates and risks of certain cancers in the general public and in hypertensive patients, the (lack of) association between angiotensin II receptor blockers (particularly valsartan) and cancer, and literature concerning NDMA/NDEA/nitrosamines and cancer/carcinogenesis. The facts and data set forth in this report are the types of facts and data on which I rely in my clinical research and on which other oncology researchers reasonably rely. In addition, I applied my education training and experience in cancer to my analysis of those facts and data. I have done (and continue to do) independent reading and literature searches pertaining to the topics above, including PubMed among other sources.

Summary of Opinions Offered

A more detailed explanation of my opinions are contained in the body of the report below. A brief summary of the major conclusions of my analysis follow:

- Cancer is not a monolithic disease but rather a collection of different diseases which have in common the uncontrolled and deleterious growth of cells in the body. Moreover, even within the broader categories, for example, of GI or GU cancers, as well as within any particular type of GI/GU cancer or other listed cancer of interest (lung, pharyngeal, breast or blood), there are important differences in terms of cancer biology, pathogenesis, risk factors, and effective treatments.

- Cancer has, at its core, a genetic etiology, often the result of inheritance (a non-modifiable risk) but more commonly a result of somatic alterations that can occur any time after conception and after birth. Some of the possible causes and risk factors contributing to non-inherited cancer (potentially modifiable risks) can be environmental, such as the common examples of prolonged exposure to tobacco smoke, asbestos, or the harmful prolonged radiation of the sun. In most cases, however, the actual cause of a particular cancer cannot be definitively determined.

- Cancer development generally takes several years and often many decades to fully develop, depending on the type of cancer and the etiology of that cancer.

- As an initial step in an analysis whether an external exposure causes any type of cancer, the human epidemiological data must establish a valid association. Even a valid epidemiological association, however, does not establish causation. To support a causal conclusion, epidemiological evidence must be well-designed and

well-conducted, statistically significant, replicated, and consistent to a reasonable degree across independent studies, among many other well-recognized criteria.[1] In the case of VCDs, upon my review it is my opinion that such evidence does not support the conclusion that VCDs in general, nor the VCDs identified to have trace levels of an NDMA and/or NDEA impurity, are associated with nor causative of any particular cancer, including any particular GI or GU cancer, nor lung, pharyngeal, breast, or blood cancer.

- While animal data and dietary data can contribute to the basis upon which to conclude that an exposure causes a particular outcome, in the case of VCDs identified to have trace levels of an NDMA impurity, the available data provides no such evidence that it is carcinogenic in humans at the exposure level and duration of these VCDs during the less than 4 years of potential exposure from late 2014 to the mid-summer of 2018.

- Data pertaining to NDMA/NDEA do not permit the conclusion that VCDs containing trace amounts of those impurities cause cancer. While there is much controversy in the medical and scientific communities about nitrosamines generally, and NDMA in particular, regarding whether exposure to such molecules increases the risk of any cancer in humans, the data are, at best, inconclusive. Moreover, since dose, duration of exposure, and pharmacokinetic issues including DNA repair are important considerations to understand whether a drug or chemical represents an increased cancer risk, that there may be some trace level of NDMA in certain formulations of VCDs cannot alone demonstrate that there is an increased risk of any type of cancer associated with exposure to those medications.

- The United States Preventive Services Task Force (USPSTF) publishes recommendations on whether to screen asymptomatic individuals for a given cancer, and under which scenarios this screening is or is not appropriate, or when there is insufficient data (for which the recommendation is not to do so). Other than a few cancer types (colorectal, breast, cervical cancers meeting age criterion, along with prostate and lung cancers and colorectal cancers at younger age that meet certain limited criteria) there are no generally accepted recommendations to actively screen asymptomatic patients for any other cancer. There are no specific indications to screen individuals any differently for those patients who are known to have taken VCDs identified to have trace levels of an NDMA or NDEA impurity.

- After consideration of the totality of available data, the scientific evidence does not support the conclusion that VCDs, and particularly the VCDs identified to have trace levels of an NDMA impurity, are associated with or cause any form of cancer (including the stated GI, GU, lung, pharyngeal, breast, or blood cancers) in humans at the exposure levels relevant for this litigation. Moreover, there is insufficient evidence that patients known to have been exposed to any VCD identified to have trace levels of an NDMA or NDEA impurity should undergo any surveillance outside the regular recommended surveillance for any given cancer type.

All of the opinions expressed in this report are held to a reasonable degree of medical and scientific certainty. In forming my opinions, I have relied on my training, expertise, and experience, as well as my review and consideration of the literature and other documents referenced in my report and/or listed in Exhibit B, including expert reports submitted by plaintiffs, and the sources cited therein. Citations to specific sources are offered as endnotes in the text of this report, where I believed it necessary to reference a specific source; otherwise, my opinions draw on a combination of the reference sources listed in Exhibit B, my own clinical experience, and my general medical training, knowledge, and ongoing review of medical and scientific literature. Exhibit B is not intended to be an exhaustive list of all source materials I considered or knowledge I had available to me in forming these opinions.

This report is not intended to set forth every opinion that I might have or develop in this litigation, and I reserve the right to supplement my list of source materials and/or to amend or supplement these opinions if additional information becomes available. I also reserve the right to respond to and rebut any information, testimony, or document(s) produced during discovery, which I understand is ongoing, and to respond to any opinions offered by Plaintiffs' experts at their depositions or at trial. Further, as requested by counsel this report contains my opinions regarding general causation only. It does not contain case-specific opinions or opinions concerning the cause of any specific plaintiff's cancer, liability, damages, or other defenses, which opinions I reserve the right to offer at a later time and through a subsequent report.

Attached as Exhibit C is a fee schedule, which sets forth my customary hourly rate for expert witness services, which is applicable to my work in this litigation.

Attached as Exhibit D is a list of cases in which I have previously given expert testimony in the past four years.

3. Introduction to Cancer

Cancer is the abnormal and uncontrolled growth of cells in the body.[2] Cancer cells are a distorted version of a normal cell – it is well-established that cancer arises from alteration of one or more cancer-related genes due to change of the DNA sequence and/or changes in the amount of DNA (amplification/deletion), or the expression of the gene itself (through epigenetic changes).

Cancer-related genes can be one of two main categories: tumor suppressor genes or oncogenes. Tumor suppressor genes are the 'brakes' in the system, and signal for cells to stop dividing/growing; if there is severe damage to the cell, they signal for it to die (apoptosis or senescence).[3] Oncogenes are the 'gas pedal' of the system, signaling for cells to divide, increase in number, and grow in size, and also some oncogenes signal the cell to migrate to other areas in the body.[2] Normally, tumor suppressors and oncogenes signal in concert and in equilibrium with each other to maintain a balance, called homeostasis. If there is a wound, nearby cells will be signaled to divide, grow, and migrate to the wound to heal it, but when healed, the cells will return to steady-state. Cancer cells signal to grow inappropriately, due to altered DNA, and behave like a wound that never stops healing.[4] Cancer cells continue to grow inappropriately and the ratio of cell growth to cell death increases, and therefore often cancer masses will form, referred to as 'tumors'. However, some tumors grow as single invasive cells

in the absence of classic tumor formation, called diffuse type tumors, such as signet ring gastric cancers.

Although different cancers from different sites and tissues of the body have different sets of altered genes causing the cancer, ultimately, all cancers are caused by alterations in DNA.[5] However, not all alterations in the genes are pathogenic (i.e. the alterations must inactivate tumor suppressors or active oncogenes inappropriately in order to be pathogenic; if they do not, they are considered 'passenger' mutations without function). Moreover, even pathogenic alterations can be 'fixed' by DNA repair. It is only those pathogenic alterations of the DNA that remain 'unrepaired' within cancer-related genes that are problematic, and these DNA alterations may be either inherited, induced by environmental factors, from random DNA replication errors, or a combination of these factors. A carcinogenesis model has been described for various cancers specifying common genes altered and the sequence in which this occurs over a period of several years.[5] It has been estimated that at least half of the genetic changes occur in precursor cancer cells prior to formation of any tumor mass.[6]

Inherited pathogenic alterations, called germline alterations, can be from a single highly penetrant gene (e.g. a tumor suppressor like the APC gene in colorectal cancer),[7,8] or they can be weaker penetrance and also can be multifactorial (multiple causative genes, but each contributing to the develop of cancer to a small degree) and more difficult to discern. A germline event(s) is present prior to the formation of the zygote (the one cell made up of DNA that is half from one parent and half from another parent, also known as a fertilized egg) in the DNA of one (or both) parents. It is estimated that inherited genetic factors are causative or contributory to approximately 5-15% of cancers, depending on the cancer type. Inheriting an altered pathogenic gene usually leads to the onset of a cancer at a younger age, due to the carcinogenesis model shifting earlier in time (i.e. the cancer development gets a 'head start' right from development).

On the other hand, somatic alterations are those that occur after conception of a zygote, through gestational development, and then after birth and through an individual's lifetime.[6,9,10] Somatic genetic alterations can occur from environmental exposures and/or from random DNA replication errors, also referred to as stochastic effects associated with the lifetime number of stem cell divisions within each tissue.[10] In other words, this is why cancer is overwhelmingly a disease of older persons — as cells continue to divide over an individual's lifetime, there are more opportunities for random mutations to occur and accumulate, which accumulation ultimately could lead to cancer. Reports have estimated that stochastic random genetic alteration over time can account for up to two thirds of cancers. In other words, the lifetime risk of cancers of many different types is strongly correlated (0.81) with the total number of divisions of the normal self-renewing cells maintaining that tissue's homeostasis; this is why cancer is generally associated with older age.[9] These results suggest that only approximately one third of the variation in cancer risk among tissues is attributable to environmental factors or inherited predispositions.

Environmental factors that contribute to the cause of cancer have been described, and can be specific to certain cancer types.[11] Environmental factors include aspects of lifestyle, economic, and behavioral exposures. Poor diet,[12,13,14] inactivity and sedentary lifestyle,[15,16,17,18] and

obesity[19,20] and metabolic syndrome[14] have each been associated with carcinogenesis. Some specific foods are linked to specific cancers.[21]

Importantly, hypertension has been associated with increased cancer risk and cancer mortality, particularly as it also tracks and closely associates with other cancer-related risk factors of smoking, alcohol use, obesity, diabetes, diet, and other factors. After adjusting for these known cancer risk factors, however, hypertension is also potentially an independent cancer risk factor in a number of tumor types including renal (kidney), colorectal, breast, esophageal, liver, and uterine cancers.[22,23,24]

Broadly speaking, any factor that may alter one's DNA sequence could contribute to carcinogenesis and the ultimate development of cancer and can be referred to as a carcinogen.[25] Mutagens are substances or agents that cause DNA changes, and carcinogens are mutagens that promote DNA changes leading to cancer. Mutagens that merely cause changes to the DNA which ultimately do not lead to the development of cancer are not carcinogens. Tobacco smoke, for example, is common and well-known to contain over fifty carcinogens, including hydrocarbons.[26] In addition to chemicals, radiation and radioisotopes are carcinogens.[27] Infections with certain viruses, bacteria, and worms are also known carcinogens.[28,29] Endogenous or exogenous hormones drive cell growth and are also known carcinogens. Importantly, however, human cells are continually bombarded with agents that can alter DNA, without leading to cancer. In some cases, no mutation occurs, despite exposure to a mutagen; in othercases, mutations do occur, but do not lead to cancer. Many mutations impact non-coding DNA and have no impact on cancer development; other mutations are corrected by cellular mechanisms before the cell divides, preventing carcinogenesis.

The International Agency for Research on Cancer (IARC) has listed groups of agents into categories (Group 1, 2A, 2B, 3, 4) as follows, based on the strength of available evidence supporting designating as a human carcinogen[29]:

> Group 1: the agent (mixture) is definitely carcinogenic to humans. The exposure circumstance entails exposures that are carcinogenic to humans.
>
> Group 2A: the agent (mixture) is probably (product more likely to be) carcinogenic to humans. The exposure circumstance entails exposures that are probably carcinogenic to humans.
>
> Group 2B: the agent (mixture) is possibly (chance of product being) carcinogenic to humans. The exposure circumstance entails exposures that are possibly carcinogenic to humans.
>
> Group 3: the agent (mixture or exposure circumstance) is not classifiable as to its carcinogenicity to humans.
>
> Group 4: the agent (mixture) is probably not carcinogenic to humans.

Cancers are classified by the cell type of origin.[30] The most common cancers are carcinomas, those derived from epithelial cells, such as the mucosal lining of the GI tract. Sarcomas are

another group of cancers that arise from the connective tissue like muscle, bone, and cartilage with precursor cells called mesenchymal cells. Malignant hematopoietic cells (leukemia and lymphoma) arise from blood-forming cells in the bone marrow and or lymph tissue in the body. Other less common cell types of origin are germ cell tumors (derived from pluripotent stem cells and in tissues such as testicle and ovary), or blastomas (cancers derived from immature precursor cells or embryonic tissue).

The normal cell cycle and behaviors of each of these tissues (regular death, senescence, and/or sloughing/loss of differentiated cells in the tissue) generally would not allow enough time for the accumulation of the necessary changes that lead to carcinogenesis. Accordingly, it is generally presumed that the resident stem cells in each tissue type (which are present longer term) are the cells of origin for the cancer type(s) arising in those tissues. It takes time for the accumulation of all the genetic and epigenetic and stromal changes required for the emergence of a neoplastic (i.e. "cancerous") cell. The time required — which we have learned from years of research and modeling — accounts for the significant latency period of the carcinogenesis models of cancers in each of these tissues.[9,10,31,32]

4. Cancer Prevention, Screening, and Incidence

The incidence of cancer (all) has slightly increased for people of all ages over the last decades. In 1975, neoplasms for those less than age 65 accounted for 22% of deaths in United States, compared to 23% in 2018, the latest year for which these data are available. In those aged over 65 years, cancers caused 18% of deaths in 1975, compared to 25% in 2018. That is, one in every four deaths are due to cancer. The incidence of new cancer cases in the United States in 2018, was 1,708,921, and 599,265 people died of cancer. In one year (2018), for every 100,000 people, 436 new cancer cases were reported (4.36/1000 people) and 149 people for every 100,000 people (1.49/1000 people) died of cancer. As such, cancer is the second leading cause of death in the United States, exceeded only by heart disease (655,341 deaths in 2018). In 2020, an estimated 1,806,590 new cases of cancer will be diagnosed in the United States and 606,520 people will die from the disease.[33,34]

Cancer prevention and screening measures can decrease the incidence and mortality of some cancers.[35] Controllable lifestyle choices (avoiding smoking, inactivity, high fat diet, etc.) and avoiding known carcinogens such as radiation can help to prevent carcinogenesis – these are modifiable risk factors of cancers. This is in contrast to unmodifiable risk factors such as gender and/or age.

Because there is a latency to the development of outright invasive cancer through various stages of preneoplastic and neoplastic progression, specific screening using specific diagnostic efforts in some circumstances, such as general screening of the public for certain cancers has been implemented.[36,37] This screening has been recommended by professional medical organizations due to relatively high incidences of these cancers coupled with demonstration of improved survival in these select (relatively few) cancer types. However, most cancers do not have routine screening recommendations to date. This screening is referred to as primary screening (screening done in the public for those who have not previously had a cancer). The screening recommendations are graded by the United States Preventive Services Task Force (USPSTF) based on the strength of the evidence and the certainty level of benefit as follows:[38]

Grade	Definition	Suggestions for Practice
A	The USPSTF recommends the service. There is high certainty that the net benefit is substantial.	Offer or provide this service.
B	The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.	Offer or provide this service.
C	The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small.	Offer or provide this service for selected patients depending on individual circumstances.
D	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.	Discourage the use of this service.
I Statement	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.	Read the clinical considerations section of USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.

The following are particular general primary screening interventions of the American public which have been shown to be able to identify early preneoplastic or early stage cancers that can be treated, with consequent improvement in overall survival in these specific cancers compared to no screening, and given their incidences and risks in the American population:

- colonoscopies for colorectal cancer (age ≥50 USPSTF Grade A; age 45-49 Grade B; age 76- 85 USPSTF Grade C),[39,40]

- mammograms for breast cancer (age 50-74 USPSTF Grade B; age 40-49 USPSTF Grade C; Age ≥75 USPSTF Grade I),[41,42]

- PSA testing for prostate cancer (potentially between the ages of 55-69, with USPSTF Grade C, but Grade D for ages ≥70),[43,44]

- Pap smears for cervical cancer (ages of 21-65 with USPSTF Grade A, while <21 or >65 Grade D).[45]

Importantly, in addition to the above, there are recommendations to NOT screen for the following specific cancers in asymptomatic adults: bladder, pancreatic, ovarian, thyroid, testicular cancers each having USPSTF Grade D recommendation. Skin cancer and oral/pharyngeal screening has a USPSTF Grade I recommendation.[38]

There are a few recommended targeted screening programs for high risk individuals such as chest CT scans for current/previous heavy smokers for lung cancer (starting at the age of 55) and abdominal imaging of patients with cirrhotic livers for liver cancer. These specific targeted recommendations will be discussed below in each specific cancer subsection.

There are also a few select set of specific recommendations for higher risk individuals for some cancers to undergo primary screening at certain times. For example, genetic testing is recommended for specific high-risk individuals, as is identifying families and individuals harboring specific pathogenic germline (inherited) genetic events who then undergo intensive screening at earlier ages, which may improve early detection and treatment for these patients. In addition to carrying an abnormal gene since birth, other specific examples for the pertinent cancers where higher risk patients are recommended to be screened (and how) are discussed below in each specific subsection. Some examples which would put a patient at higher risk includes a patient who has a personal history of cancer or an illness that is known to predispose to cancer with high rate (eg inflammatory bowel syndrome). For patients who have already had a cancer, further screening in them is referred to as secondary prevention (to identify a potential second cancer earlier).

The reason for guidelines on cancer screening is that there are potential risks and negative consequences to screening including patient anxiety and false positives.[32,35,36,37,38,39] There is no basis in the USPSTF screening recommendations for someone to subject themselves to enhanced screening for the types of cancers at issue in this litigation, given that there is lack of definitive evidence of increased cancer risk at the levels of NDMA found in VCDs, or that screening in this situation has any utility, The risks and negative consequences of cancer surveillance outside of what would already be recommended routinely is greater than any risk from NDMA. It is notable, however, that the vast majority of patients taking antihypertensive medications, including VCDs and VCDs with NDMA impurity, would be older and will already be receiving the routine recommended screening for the cancers noted above by the USPSTF guidelines.

5. Cancer Symptoms, Diagnosis, and Staging

Cancer is diagnosed, usually, with the presence of various symptoms that are a consequence of the primary site of origin of the cancer and/or from sites of metastatic spread.[46] Solid tumor cancers (of epithelial, mesenchymal, germ cell or blastoma origin, along with subgroups of lymphomas) often cause localized symptoms due to mass effect or involvement at the site of origin that are often specific to that site. This can include pain, discomfort, and/or negative effects on the function of the organ site of origin. Hematologic malignancies (referred as 'liquid' cancers) often cause cytoplasias (blood cell abnormalities) that lead to their dysfunction and consequent symptoms such as fatigue from anemia, bleeding from thrombocytopenia, and infection from white blood cell dysfunction or leukopenias. Cancers can also be identified through routine screening of high-risk or average risk patients through screening measures (when appropriate and recommended), in the absence of symptoms. Also, cancers can be identified incidentally when evaluating other unrelated issues.

Diagnostic tools include physical exam and vital signs, laboratory studies, and various imaging studies including ultrasounds (US), computerized tomography (CT scans), magnetic resonance imaging (MRI), and positron emission tomography (PET scans), and other specialized imaging procedures. A number of scoping procedures to visualize affected organs are also used, including endoscopies (GI from above, EGD; GI from below, colonoscopy), bronchoscopies, and cystoscopies. Sometimes surgical explorations are required including laparoscopies or video-assisted thoracoscopic surgeries (VATS). Ultimately, biopsies of affected tissue and evaluation under the microscope by a pathologist is generally used to arrive at the definitive diagnosis of cancer.

With the diagnostic tools above, cancers are staged to determine the extent of the disease throughout the body. Early stages (for solid tumors) are those that are confined to the site of origin. Locally advanced cancers are those that are confined to the site of origin but advanced to regional structures and lymph nodes around the site of origin. Advanced metastatic cancers are those that have spread to distance sites away from the site of origin. Cancers are staged because this determines the prognosis of the cancer and also the optimal treatment approaches. Generally, the higher the disease stage at diagnosis, the worse the overall prognosis.

6. Cancer Treatment

Treatments for cancer vary by cancer type, stage, and patient characteristics. Generally cancers of early stages have good prognoses with local therapies alone, including surgery and/or radiation. Cancers that are locally advanced often require 'adjuvant' (or 'neoadjuvant') systemic treatments like chemotherapy or immunotherapy in addition to the localized treatments, since they have a higher risk of having occult (undetectable but present) micro-metatastatic disease. Treatments such as chemotherapies, targeted therapies and immunotherapies can enhance the cure rates in these situations.

Cancers that are metastatic generally have relatively poor prognosis and, to date, are mostly incurable. In the metatastatic setting (Stage IV), therapies including chemotherapies, targeted therapies and/or immunotherapies are palliative with intention to decrease/prevent cancer-related symptoms and improve survival time, but they are not curative. Different

chemotherapies, targeted therapies, and/or immunotherapies are used for different cancers and subtypes of cancers.

Ideal treatment for any given scenario is applied to a given patient's context. That is, if a patient has a poor performance status (unable to perform daily activities on their own without help) and multiple comorbidities (e.g. heart disease, uncontrolled blood pressure, neurologic dysfunction, liver dysfunction, low blood counts etc), then it is often not possible to provide ideal therapies due to these competing problems, and these patients tend to have worse prognosis overall as a consequence.

I also reviewed the expert report offered by Dr. Panigrahy in this litigation. In that report, Dr. Panigrahy obliquely comments that "continued exposure to NDMA and/or NDEA can… otherwise interfere with cancer therapy." (See Panigrahy Report, at p. 221). No citation is provided for that assertion and it is unclear what he intends to say; I am aware of no literature supporting that proposition. Neither exposure to NDMA/NDEA, nor exposure to VCDs potentially containing NDMA/NDEA is something I consider when deciding treatment options or recommending a specific course of treatment for any of my oncology clinic patients. I am unaware of any specific consequence that prior NDMA or NDEA exposure could have on the efficacy or tolerability of any cancer therapy or any literature that would support Dr. Panigrahy's theory.

7. Post-Treatment Cancer Surveillance

For patients with cancers that are treated with curative intent, surveillance is performed after completion of the prescribed therapy in order to identify a recurrence of the original cancer. Surveillance usually entails regular visits with the patient's provider every 3-6 months, along with laboratory and imaging tests periodically, in order to identify recurrences and to act upon them before they become symptomatic, sometimes with curative intent, and most often still with palliative intent. After 5-10 years of surveillance (depending on the cancer type and circumstances), the risk of recurrence usually decreases such that patients may be followed per routine with their general healthcare provider.

8. Specific Cancers of Interest

8a. Introduction to Gastrointestinal Cancers

In 2019, approximately 328,030 new cancers of the digestive system will be diagnosed in the United States, which makes it the most common physiologic system afflicted by cancer and more common than breast cancer (n = 271,270), lung and respiratory tract cancers (n = 246,440), and genitourinary cancers (n = 295,290). Approximately 165,460 patients will die annually of GI malignancies, including 51,020 patients with colorectal cancer, 45,750 patients with pancreatic cancer, 31,780 patients with liver and intrahepatic bile duct cancers, and 27,220 patients with gastroesophageal cancers (GECs).[33,47,48] The incidences of these cancers in 2018 were as follows: colorectal cancer 141,074 (age adjusted rate 36.5/100000 people); pancreatic cancer 52,546 (age adjusted rate 13/100000 people); liver and bile duct 34,638 (age adjusted rate 8/100000 people); gastroesophageal cancers 42465 (age adjusted rate 11/100000 people).

The total incidence, then, for GI cancers in 2018 was 270,723 (age adjusted rate 68.5/100000 people).[34]

The spectrum of diseases encountered in this field varies from rather indolent malignancies, such as low-grade neuroendocrine tumors with overall survival (OS) measured in years, to very aggressive and rapidly fatal cancers, such as pancreatic and hepatocellular carcinomas, for which, in advanced stages, survival is typically measured in months to a year. Several cancers of the digestive tract are linked to hereditary syndromes that require genetic counseling of patients and family members.

Introduction to Gastroesophageal Cancer (GEC):

GECs exhibit great variation in histology, geographic distribution, and incidence over time. Recent classification generally comprises three main gastroesophageal cancer subtypes, reflecting our current understanding of the anatomy, history, etiology and molecular basis of these cancers: (1) gastroesophageal junction (GEJ) or esophageal junction (EJ) adenocarcinomas; (2) esophageal squamous cell cancer (SCC); and (3) distal gastric AC.

Numerous histologic subtypes have been described, particularly pertinent to gastric AC but also for GEJ AC, including histologic differentiation (ie, well, moderate, poor), Lauren classification (ie, intestinal, diffuse, mixed type), presence of signet-ring cells or not, and a whole host of other subtypes in the WHO criteria.[49] Despite the noted differences between GEJ AC and gastric AC, these two subtypes are often grouped together as gastroesophageal adenocarcinoma (GEA) in both the locally advanced and metastatic settings, when considering therapy.[50,51]

In the United States, GECs, together, represent the third most common GI cancer (after colorectal and pancreatic), with the third highest mortality rate.[34,52] Worldwide, they are the third most common cancer and second leading cause of cancer mortality.[48] The risk factors for the various subgroups of GEC are quite different with esophageal SCC strongly associated with smoking and alcohol use, much like lung SCC and pharyngeal SCC. Historically, the most common types of GECs were esophageal SCC of the upper to middle esophagus and distal gastric AC.[53] However, during the past three to four decades, particularly in western countries, including the United States, the incidences of esophageal SCC and distal gastric AC have decreased. In contrast, the incidence of GEJ AC has reciprocally increased rapidly during this same period in the Western world, paralleling the rise of gastroesophageal reflux disease (GERD), obesity, diabetes, high fat diet, and metabolic syndrome in the general population. These cancers are also notably and significantly associated with patients with a high body mass index.[54,55]

<u>Esophagogastric Junction Adenocarcinoma</u>

GEJ ACs typically arise in metaplastic epithelium—a condition known as Barrett esophagus (BE).[55] Murine carcinogenesis models suggest migration of precursor cells from the gastric cardia proximally into the distal esophagus.[56] The incidence of BE is 10% to 20% among symptomatic patients who undergo endoscopy and 30% to 50% for patients with peptic strictures. Risk factors associated with BE include GERD, white or Hispanic race, family risk,

male sex, advanced age, smoking, diabetes mellitus, Western diet, and obesity and metabolic syndrome.[55,57,58] However, there is heterogeneity in carcinogenesis and not all tumors arise within a BE background. Approximately 60% of GEJ AC cases have evidence of precursor BE. In a nationwide population study from Denmark, the relative risk of AC among patients with BE was 11.3 (95% CI, 8.8 to 14.4) compared with the risk in the general population.[59] The annual risk of GEJ AC was 0.12% (95% CI, 0.09 to 0.15).

There is an inverse association between Helicobacter pylori infection and GEJ AC, potentially as a result of the reduced acidity associated with atrophic gastritis.[60] Whether rigorous medical management of GERD with long-term use of proton-pump inhibitors (PPIs) can affect the natural history of the disease or the development of malignancy has long been debated. A recent, large prevention study, ASPECT, evaluated this question in patients with BE ≥ 1 cm and no HGD or esophageal AC.[61] A total of 2,563 patients were randomly assigned to high-dosage (40 mg twice daily) or low-dosage (20 mg once daily) esomeprazole PPI acid suppression, alone or combined with aspirin 300 mg/d. The primary composite end point was time to all-cause mortality, esophageal AC, or high-grade dysplasia. The combination of aspirin with high-dose PPI had the strongest effect, compared with low-dose PPI with no aspirin.[61] Another recent, large, population-based retrospective analysis of Nordic countries evaluating 942,906 patients with GERD reported that medical and surgical treatments of GERD were associated with a similar reduced esophageal AC risk, with the risk decreasing to the same level as that in the background population over time, supporting the hypothesis that effective treatment of GERD might prevent esophageal AC.[62] Other than antireflux medication[61] and antireflux surgery,[62] the typical treatment of patients with BE is surveillance using upper endoscopy and collecting a biopsy specimen to examine tissue for evidence of dysplasia.[57]

Gastric AC

In the United States, gastric AC is seen twice as often in men as in women and more frequently in black men than in white men, and its incidence increases with age, starting at 50 years.[63] The incidence of gastric AC has varied considerably during the past century. In the United States, the incidence of gastric AC has decreased approximately 75% during the past few decades.[52] Although gastric AC rates have declined worldwide, it is still prevalent in regions of the world where the storage of fresh foods and the quality of water are poor and in some industrialized nations as well (e.g., Japan).[64] Gastric AC is a major health issue in Japan and Korea, and both countries have nationwide screening programs. In Japan and Korea, gastric AC is associated with a better prognosis than in western cultures and thought to be multifactorial including different disease biology, different treatment approaches, and other unknown factors. When controlling for baseline tumor characteristics, patient demographics, and surgical factors, there is a difference in survival that remains unexplained.[65] Studies of migrant populations have supported evidence for the effect of environmental influences on the development of gastric AC.[66,67] Factors associated with an increased risk of gastric AC include nutritional factors such as high salt and high fat diets, a diet low in vitamins A and C, the consumption of large amounts of smoked or cured foods, lack of refrigerated foods, and poor-quality drinking water.[68] Occupational exposure to rubber, asbestos and coal also increases the risk.[75,69,70,71,238] Cigarette smoking,[72] H. pylori infection,[73,74] Epstein-Barr virus,[75] radiation

exposure, and prior gastric surgery for benign ulcer disease also have been implicated as risk factors.[76] Together, these data support the concept that gastric AC is often influenced by nutritional, socioeconomic, and medical factors rather than dominated by genetic predisposition. Awareness and decreased exposure to these factors have contributed to the decline in incidence and mortality rate of gastric AC in the United States.

Genetic risk factors include type A blood, pernicious anemia, a family history of gastric AC, hereditary nonpolyposis colon cancer (HNPCC), Li-Fraumeni syndrome, and hereditary diffuse gastric cancer (HDGC) caused by mutations in the E-cadherin gene, CDH1.[77,78,79] HDGC is a genetic predisposition syndrome characterized by a family history of gastric AC characterized by poorly cohesive, diffuse-type histology, often with early onset of disease (generally younger than age 40 years); it accounts for <5% of gastric cancers. The cumulative risk of the development of diffuse gastric AC by the age of 80 years for CDH1 mutation carriers is 70% for men and 56% for women. Women are also at higher risk for the development of lobular breast cancer, with a cumulative risk of 42% by age 80 years. Individuals with a germline mutation in CDH1 should undergo a risk-reducing prophylactic gastrectomy to prevent future development of HDGC.[80] The optimal timing of prophylactic gastrectomy is unknown and is usually highly individualized. The current consensus is that the procedure should be discussed and offered to carriers of pathogenic germline CDH1 mutation in early adulthood, generally between ages 20 and 30 years.

Results from several studies have demonstrated an increased likelihood of H. pylori infection in patients with gastric AC, particularly cancer of the distal stomach.[73,74] H. pylori infection is relatively common. About 30 to 40% of people in the United States get an H. pylori infection.[68] Most people get it as a child. It is thought that H. pylori spreads by unclean food and water, or through contact with an infected person's saliva and other body fluids; therefore it can track with families living together in close proximity. H. pylori usually does not cause symptoms. But it can break down the inner protective coating in some people's stomachs and cause inflammation. This can lead to gastritis or a peptic ulcer. Although cancer does not develop in most people with H. pylori infections, the known increased risk for patients to develop cancer who are infected has raised the issue of whether treatment of H. pylori might decrease the risk of gastric AC. Although the role of H. pylori in gastric carcinogenesis is well defined, no definitive evidence shows that mass eradication could reduce the incidence of gastric cancer.[81] A large Chinese study showed no benefit in the prevention of gastric AC with the eradication of H. pylori.[82] By contrast, a meta-analysis suggested that eradication, indeed, could reduce the risk of gastric AC.[83,84] At present, treatment of patients with this infection is reserved for those with demonstrated ulcers, gastritis, or other symptoms.[60]

Clinical presentation, diagnosis and staging of GECs

The most common clinical presentation of esophageal SCC and GEJ AC is dysphagia (problems swallowing). Cachexia and substantial weight loss are complications of this presenting symptom, which cause many patients to be debilitated at the time of the diagnosis. Another common presentation is occult or frank bleeding (usually manifested by melena, iron-deficiency anemia, and fatigue).[64] Other symptoms include treatment-refractory heartburn. It is not uncommon that patients have symptoms of chronic heartburn and dyspepsia, having

taken over the counter antacid and heartburn medications for years before finally being evaluated and ultimately being diagnosed with gastroesophageal cancer and its precursor lesions as the etiology of those symptoms. Patients with more proximal tumors can have tracheobronchial invasion and may present with laryngeal nerve paralysis, cough, and/or post-obstructive pneumonia.[85]

Because of vague symptoms that go unaddressed for some time, it is unfortunately common for patients with GEA to present with synchronous metastatic disease when symptoms become more severe, persistent, and compounded by metastatic spread. Common sites of disseminated disease are liver, lung, distant lymph nodes, bone, and peritoneum. Carcinomatoses are common and seen in approximately 30% of patients with GA and 10% to 15% with GEJ AC (particularly diffuse and mixed-type histology, and tumors with signet-ring features), and result in the formation of ascites and abdominal pain culminating in severe anorexia, dysfunctional bowel, and, ultimately, frank partial or complete bowel obstructions.[64]

Introduction to Pancreas Cancer:

Exocrine pancreatic cancer is a substantial health problem in the United States, with an annual incidence of 56,770 cases and death occurring in 45,750 patients annually.[33,48]. The nonhereditary risk factors for pancreatic cancers include older age, diabetes, chronic pancreatitis, intraductal pancreatic mucinous neoplasms, cigarette smoking, obesity, physical inactivity, and a diet high in saturated fats.[86] More recent data suggest pathogenic germline alterations may be present in up to 20% of unselected exocrine pancreatic cancers and has led to the recommendation for universal testing of patients with pancreatic cancer for germline mutations regardless of family history.[87 ,88]

Symptoms associated with pancreatic cancer at the time of presentation commonly include abdominal pain with or without back pain, cachexia, and/or jaundice.[89,90] Initial symptoms are often vague and can vary based on location, with pancreatic head lesions more likely to cause jaundice, and tail lesions, which often can be asymptomatic and, thus, delay diagnosis. When evaluating patients with adult-onset diabetes without other risk factors or worsening diabetes without an obvious cause, physicians should consider pancreatic cancer as a possible diagnosis.[91] Although pancreatic cancer is staged using the standard TNM methodology, in practice, it is often classified as resectable, borderline resectable, locally advanced unresectable, or metastatic.

Introduction to Hepatobiliary Cancer:

Primary hepatobiliary cancers are a heterogenous group of cancers, which include hepatocellular carcinomas (HCCs), cholangiocarcinomas, and gallbladder cancers, and they represent the highest global incidence of solid-organ tumors and are responsible for approximately 1 million deaths annually, although they are less common in western cultures (particularly HCCs).[33,48] The risk factors for HCC are well known and include cirrhosis of any etiology.[92,93,94] Hepatitis B virus infections account for approximately 60% of all liver cancer incidence in developing countries and for approximately 23% of liver cancer in developed countries; the corresponding percentages for hepatitis C virus infections are 33% in developing

countries and 20% in developed countries. Hepatitis B infection can be decreased by vaccination. Hepatitis C now has effective therapy to eradicate the viral infection, which may lead to fewer cases of HCC in the coming years. In the United States and several other western countries with low-risk populations, alcohol-related cirrhosis and, nonalcoholic fatty liver disease also referred to as nonalcoholic steatohepatitis (NASH), associated with obesity, are thought to account for most liver cancers.[93,94] The metabolic syndrome, which is defined to include diabetes (hyperglycemia, or high blood sugar), obesity, dyslipidemia (high serum triglycerides and/or high cholesterol), hypertension,[95] and microalbuminia, is increasing in the United States,[96] and becoming a more common risk factor for all cancers,[97,98,99] including liver cancer via NASH.[100,101]

The total mortality from HCC in the United States has been increasing due to alcohol-related cirrhosis and, possibly, nonalcoholic fatty liver disease, despite the encouraging reduction in mortality associated with hepatitis C virus–related HCC.

Biliary tract cancers (cancer of the bile duct and gallbladder) include a diverse group of cancers, including intrahepatic cholangiocarcinoma (IHCC), hilar cholangiocarcinoma, extrahepatic cholangiocarcinoma (EHCC), and gallbladder cancer. Historically, these were considered a uniform entity, but they now are recognized to be quite distinct in terms of etiology, molecular biology, and, most recently, treatment.[102,103,104,105] In western countries, cholangiocarcinoma is associated with metabolic syndrome/NASH,[97,100] inflammatory bowel disease, primary sclerosing cholangitis, and hepatolithiasis, whereas the liver fluke and hepatitis B virus are important risk factors in Asian countries.[106] Cholangiocarcinoma is most common in women older than 50 years. A number of risk factors for gallbladder cancer have been described and include:

- obesity/metabolic syndrome,
- female sex,
- family history,
- middle age,
- gallstones causing chronic inflammation,
- porcelain gallbladder (ie, hardened gallbladder due to calcium deposits),
- ethnicity (highest in Mexican, Lain Americans, and Native Americans),
- choledochal cysts (ie, bile-filled sacs along the common bile duct),
- gallbladder polyps,
- abnormalities of the bile ducts causing backflow, and
- primary sclerosing cholangitis.[106]

Recent molecular studies have demonstrated distinct molecular profiles between the anatomic sites and geographic or etiologic subsets.[107,108,109,110] Cancers (adenocarcinomas) of the extrahepatic bile duct and gallbladder are relatively rare, with only 11,740 cases diagnosed annually in the United States, resulting in approximately 3,830 deaths annually.[33,111]

Unfortunately, US statistics do not give specific numbers for IHCCs but classify them under “hepatobiliary tumors”; the actual incidence of biliary cancers as a whole is definitely higher, perhaps approaching the incidence of esophageal cancers, with approximately 15,000 cases

per year.[112] ACs of unknown primary site involving the liver are more commonly recognized as primary IHCCs, which has also led to an increase in incidence of the disease.[113]

There is a wide array of presentations of HCC, from asymptomatic disease found at screening to decompensated cirrhosis or paraneoplastic syndromes. Guidelines disseminated from several consensus conferences and professional organizations have recommended HCC surveillance in patients with cirrhosis who are at high risk for development of HCC.[114] Ultrasound and serum α-fetoprotein (AFP) are the most commonly used modalities for HCC surveillance. Fibrolamellar cancer is generally seen in younger patients, is much more likely to be resectable, and is less commonly associated with infection or cirrhosis.[115] In contrast, traditional HCC is found more often in men older than 65 years. Cholangiocarcinomas typically present with jaundice, pain, anorexia, abnormal laboratory test results, or with a mass evident on CT scan or ultrasound or that is visualized endoscopically.[116] Gallbladder cancer often presents as vague postprandial right upper quadrant pain and is diagnosed as gallstones, with incidental finding of gallbladder cancer at the time of resection and/or in the pathology specimen.[117] The location of the primary tumor often dictates which of these symptoms predominantly occur, such as painless jaundice with extrahepatic cholangiocaricnoma that is quite similar that seen with pancreatic cancer.

Introduction to Colorectal Cancer:

Colorectal cancers are cancers that arise in the large colon, which is comprised of the Cecum/appendix, ascending colon, transverse colon, descending colon, sigmoid colon, and rectum. The cancer precursor cells arise from the epithelial cells (the mucosal inner lining of the colon), and are carcinomas that have mucus gland differentiation, and are thus 'adenocarcinomas'. Annually, approximately 147,950 new cases of large bowel cancer will be diagnosed, 104,610 of which are colon cancer, and the remainder rectal cancer.[47]

Colon cancer etiology has been associated with a number of contributing factors,[118] including genetic syndromes,[7,8] high fat and red meat diet,[119,120,121] obesity/metabolic syndrome,[19,97,122] sedentary lifestyle,[123,124] diabetes,[125] radiation,[126] inflammatory bowel disease,[133] asbestosis,[127,128] and tobacco and alcohol.[129] It is common to have more than one of these associated risk factor, as they often track together, and it is likely that having many of these factors will heighten the risk of developing colorectal cancer.

Colon cancers start at level of an individual cell within the mucosa (the most superficial layer in the colon that serves as the inner layer of the 'tube') that acquires genetic alteration.[131] The initial pathology is the formation, usually, of a polyp.[131] A polyp is a mass of hyperplastic cells that forms a pedunculated polyp into the colon lumen. Over time accumulation of more genetic alterations in tumor suppressor and oncogenes within cells in the polyp lead to a 'transformed' and invasive component of the polyp which is malignant.[5,132] Over more time, the cancer can travel through the lymphatic system and/or the blood to spread to distant sites in the body. There is therefore a long period of time on the order of decades, generally, from inception of the colonic preneoplastic cell(s) of origin and then progression toward invasive neoplasia (stage I), and then to higher stages (stages II-IV) of the cancer. This carcinogenesis model of colorectal cancer is well-established.[5]

Multiple screening tests are available to detect adenomatous polyps and colorectal cancer (CRC) before they become symptomatic. Tests for CRC differ with regard to sensitivity and specificity, frequency of testing, evidence of effectiveness, convenience, safety, availability, and cost. A general gold standard has been colonoscopies.[39] In addition to the USPSTF colon cancer screening recommendations for average risk individuals (the general population) to initiate at age ≥45 due to the association of colon cancer risk and age, as discussed above, there are recommendations to screen at younger ages for higher risk individuals including those with family or personal history of colorectal cancer and/or a known genetic predisposition syndrome such as Lynch syndrome,[7,8] or inflammatory bowel disease.[133]

There are no medical societies that list NDMA as a risk factor for gastrointestinal cancers as a consideration of etiology (whether gastric AC, hepatobiliary, pancreatic or another type), nor do any guidelines suggest that treatment of screening/surveillance of gastrointestinal cancer is changed in any way for patients who might have been exposed to NDMA impurities in VCDs.

8b. Introduction to other Upper Aerodigestive Cancers

Upper aerodigestive cancers include lung and oralpharyngeal cancers. In 2018, the incidence of new cases of lung and respiratory tract cancers was 218,520 cases (age adjusted rate 54/100000 people) and 142,080 people died of this cancer (age adjusted rate 35/100000 people). In 2018, the incidence of new cases of oralpharyngeal cancers was 46,667 cases (age adjusted rate 12/100000 people) and 10,185 people died of this cancer (age adjusted rate 3/100000 people). Another closely related cancer, laryngeal cancer, had 12,023 new cases, and 3,777 people died of this cancer. For every 100,000 people, 3 new Laryngeal cancer cases were reported and 1 people died of this cancer.[34]

Introduction to Lung Cancer

Overall, lung cancer causes more deaths than breast, prostate, colorectal, and brain cancers combined.[33,111] Lung cancer deaths are declining in men and women, largely due to decreases in smoking. Now, however, nearly one-half of all lung cancer deaths occur in women. The term lung cancer, or bronchogenic carcinoma, refers to malignancies that originate in the airways or lung cells (parenchyma). Approximately 95 percent of all lung cancers are classified as either small cell lung cancer (SCLC) or non-small cell lung cancer (NSCLC) with the majority being NSCLC (~80-85%) vs SCLC (~15%). This distinction is required for proper staging, treatment, and prognosis. Other cell types comprise about 5 percent of malignancies arising in the lung. The main subtypes of NSCLC are adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. These subtypes, which start from different types of lung cells are grouped together as NSCLC because their treatment and prognoses (outlook) are often similar.

Similar to many cancers, advances in understanding the molecular pathogenesis of NSCLC have demonstrated that NSCLC is a heterogeneous group of diseases. Although the initial treatment of localized disease is the same generall at this time, the molecular characterization

of tumor tissue in patients with NSCLC serves as a guide to treatment both in those who present with metastatic disease and in those who relapse after primary therapy.

Smoking is by far the leading risk factor for lung cancer. About 80% of lung cancer deaths are thought to result from smoking and this number is probably even higher for small cell lung cancer (SCLC). It's very rare for someone who has never smoked to have SCLC. The risk of lung cancer for people who smoke is many times higher than for people who don't smoke. The longer you smoke and the more packs a day you smoke, the greater your risk. Cigar smoking and pipe smoking are almost as likely to cause lung cancer as cigarette smoking. Smoking low-tar or "light" cigarettes increases lung cancer risk as much as regular cigarettes. Smoking menthol cigarettes might increase the risk even more since the menthol may allow people to inhale more deeply. If you don't smoke, breathing in the smoke of others (called secondhand smoke or environmental tobacco smoke) can increase your risk of developing lung cancer. Secondhand smoke is thought to cause more than 7,000 deaths from lung cancer each year.[134]

Radon is a naturally occurring radioactive gas that results from the breakdown of uranium in soil and rocks. It cannot be seen, smelled, or tasted. Radon is the second leading cause of lung cancer in this country, and is the leading cause among people who don't smoke. Outdoors, there is so little radon that it is not likely to be dangerous. But indoors, radon can be more concentrated. Breathing it in exposes your lungs to small amounts of radiation. This may increase a person's risk of lung cancer. Homes and other buildings in nearly any part of the United States can have high indoor radon levels (especially in basements).[135]

People who work with asbestos (such as in mines, mills, textile plants, places where insulation is used, and shipyards) have a higher risk of being diagnosed with and dying from lung cancer. Lung cancer risk is much greater in workers exposed to asbestos who also smoke. It is not clear how much low-level or short-term exposure to asbestos might raise lung cancer risk. People exposed to large amounts of asbestos also have a greater risk of developing mesothelioma, a type of cancer that starts in the pleura (the lining surrounding the lungs).

Other carcinogens found in some workplaces that can increase lung cancer risk include radioactive ores such as uranium, inhaled chemicals such as arsenic, beryllium, cadmium, silica, vinyl chloride, nickel compounds, chromium compounds, coal products, mustard gas, and chloromethyl ethers, and diesel exhaust.[136] Also, air pollution in cities espcially near heavily trafficked roads may raise the risk of lung cancer.[137] Marijuana is possibly also associated with increased risk.[138, 139, 140]

Lung cancer history in the family may also lead to a higher personal risk of lung cancer – however how much is genetic versus exposure to the same environmental and household exposures is not clear.[141]

Overall, despite these many possible risks above for lung cancer, the vast majority of cases are solely due to tobacco smoking.[111] It is also notable that many other cancers are associated with tobacco smoking as discussed in other sections of this report. People with an extensive history of (or current) smoking have been shown to have improved clinical detection and lung-cancer mortality[142] via routine CT screening of the chest.[134, 143]

It is notable that smoking increased hyptertension in addition to its carcinogenic effects, and thus increases hypertensive related disease including cardiac, renal, and other hypertensive-related medical problems.[144,145,146] Therefore there is a significant and well-established relationship between tobacco use and use of antihypertensive medications, including VCDs.

Introduction to Pharyngeal Cancer

Head and neck cancers can have many different names depending on where the cancer starts. For example, cancers that start in the throat (pharynx), can be called nasopharyngeal (for the upper throat behind the nose), oropharyngeal (for the middle throat behind the mouth), or hypopharyngeal (for the lower throat). Oropharyngeal squamous cell carcinomas (SCCs) originate in the soft palate, tonsils, base of tongue, pharyngeal wall, or vallecula (the fold located between the base of tongue and the epiglottis). Historically, tobacco and alcohol were the principal risk factors associated with oropharyngeal cancer. However, there has been a shift in the epidemiology of this disease, with a significant increase in cases due to human papillomavirus (HPV) infection and a decrease in cases associated with tobacco and alcohol.[147, 148] Infection with certain types of HPV can cause some forms of cancer, including cancers of the penis, cervix, vulva, vagina, anus, mouth, and throat. In certain other areas of the world, many people chew betel quid, which is made up of areca nut (betel nut), spices, lime, and other ingredients. Many people in these areas also chew gutka, a mixture of betel quid and tobacco. People who chew betel quid or gutka have a recognized increased risk of cancer of the mouth. Other associated factors include obesity, higher age, diet low in fruits and vegetables.

There are no medical societies that list NDMA as a risk factor for upper aerodigestive cancers as a consideration of etiology, nor do any guidelines suggest that treatment of screening/surevillance of upper aerodigestive cancer is changed in any way for patients who might have been exposed to NDMA imuprities in VCDs.

8c. Introduction to Genitourinary Cancer

"Genitourinary cancers" encompass a variety of heterogeneous cancers that arise from the urinary tract or urogenital system (urinary bladder, ureters, prostate, penis, uterus, cervix, and vagina). In 2018, the incidence of new cases of genitourinary cancers of interest (urinary bladder, kidney, prostate and uterus) combined was 413,155 cases (age adjusted rate 170/100000 people) and 73,501 people died of these cancers (age adjusted rate 32/100000 people).[34]

Introduction to Bladder Cancer

Bladder cancers are the most common genitourinary malignancy in both men and women. In 2018, the incidence of new cases of urinary bladder cancers was 77,443 cases (age adjusted rate 17/100000 people) and 14,134 people died of this cancer (age adjusted rate 4/100000 people).[34] Bladder cancers are broadly categorized as urothelial and non-urothelial, where approximately 90% of bladder cancers are urothelial.[149] Non-urothelial bladder cancer

accounts for less than 5 percent of all bladder tumors, and approximately 90 percent of non-urothelial bladder cancers are epithelial in origin, and these include squamous cell carcinoma, adenocarcinoma, and small cell carcinoma. Non-epithelial tumors include sarcoma, carcinosarcoma, paraganglioma, melanoma, and lymphoma.

Unmodifiable risk factors of bladder cancer include age, sex, and ethnicity. Bladder cancer is typically diagnosed in older individuals. A majority (approximately 73 percent) of patients with bladder cancer are older than 65 years of age.[150] The age of onset is younger in current smokers than in never smokers.[151] Although the overall incidence of bladder cancer is lower in females and African Americans, these groups have more advanced-stage tumors at presentation compared with Caucasian males.[152] While there appears to be a small increased risk in relatives of those with bladder cancer, particularly in cancers diagnosed before age 60, the risk is influenced by smoking.[153] Lynch syndrome, classically a genetic predisposition to colorectal cancer, uterine cancer, and gastric cancer, also includes bladder cancer, which 5% of Lynch syndrome patients experience.[154]

Modifiable risk factors of bladder cancer include cigarette smoke being the most important contributing factor to the overall incidence of urothelial cancer in western countries.[155] This database included over 465,000 individuals followed from 1995 to 2006 in the United States. For current smokers, there was a significant increase in the risk of bladder cancer for both males and females (multivariate adjusted hazard ratios [HRs] 3.89 and 4.65, respectively). Although there was an attenuation of risk in former smokers, the risk remained significantly elevated (HRs 2.14 and 2.52 for males and females, respectively). There was a small but statistically significant increase in the incidence of bladder cancer among males who smoked a pipe or cigars but not cigarettes (HR 1.29). Smoking cessation also appears to decrease the recurrence rate for patients with non-muscle-invasive bladder cancer even after the diagnosis.[156]

In addition to cigarette smoke, occupations that have been linked to an increased risk of bladder cancer include metal workers, painters, rubber industry workers, leather workers, textile and electrical workers, miners, cement workers, transport operators, excavating-machine operators, and jobs that involve manufacture of carpets, paints, plastics, and industrial chemicals. Compounds potentially linked to bladder cancer include benzene, polyaromatic hydrocarbons, paint components, hair dye components and diesel exhausts, among others.[157]

Other risk factors include chronic and recurrent bladder infections, HPV infection, previous radiation to the bladder, previous exposure to cyclophosphamide chemotherapy/ immunosuppressant, and previous bladder surgery (augmentation cystoplasty). Overall, despite these many possible risks above for bladder cancer, the vast majority of cases are solely due to tobacco smoking.

It is notable that a positive association was observed between hypertension and urinary bladder cancer. In this study of 39,618 patients, during a total follow-up duration of 380,525 and 372,020 person-years in the hypertension and comparison non-hypertension groups, 248 and 186 patients developed UB cancer, respectively, representing a 32% increase in the risk (aHR, 1.32; 95% CI, 1.09-1.60). A separate population-based study using a similar dataset found no

impact from antihypertensive use on the risk of bladder cancer, after controlling for age, sex, urbanization level, occupation, income, diabetes, dyslipidemia, stroke, coronary heart disease, chronic obstructive pulmonary disease, alcoholism, and alcoholic liver damage derived a neutral risk (adjusted HR = 1.19; 95% CI, 0.80–1.77) in patients receiving antihypertensive agents versus those who were not.[158] This suggests that hypertension and its associated factors/comorbidities are linked with bladder cancer development.

Introduction to Kidney (Renal) Cancer

In 2018, the incidence of new cases of kidney cancers was 65,759 cases (age adjusted rate 18/100000 people) and 16,641 people died of this cancer (age adjusted rate 4/100000 people).[34] Renal cell carcinomas (RCCs), which originate within the renal cortex, are responsible for 80 to 85 percent of all primary renal neoplasms. Transitional cell carcinomas of the renal pelvis are the next most common (approximately 8 percent). Other parenchymal epithelial tumors, such as oncocytomas, collecting duct tumors, and renal sarcomas, occur infrequently. The most common histologic pattern of RCC is clear cell (75 to 85 percent). Papillary and chromophobe tumors constitute 10 to 15 and 5 to 10 percent, respectively. The VHL gene is found on chromosome 3 (3p25 to 26) and plays a pivotal role in the development of clear cell RCC in patients with VHL disease and sporadic RCC.[159,160]

Unmodifiable risk factors of RCC include gender, where males are diagnosed twice as commonly as females.[160] Age is another risk factor, where RCC occurs predominantly in the sixth to eighth decade of life with median age at diagnosis around 64 years of age.[161] The risk of a second, metachronous RCC is increased in patients who have been treated for one renal cancer. This increased risk is most pronounced with younger age at the first RCC, suggesting that early onset renal cancer has a genetic component.[162] There are documented familial predispositions with RCC.[163] Patients with inherited polycystic disease may have an increased risk of RCC (as well as liver and colon cancer), even in the absence of kidney dysfunction or end-stage kidney failure.[164]

Modifiable risk factors of RCC include smoking,[165] hypertension,[166] obesity,[167] hemodialysis patients with acquired polycystic kidney disease,[168] and occupational exposure, including cadmium, asbestos, and petroleum byproducts.[169] Prior radiation and chemotherapy have also been associated with RCC.[170,171]

It is notable that a positive association was observed between hypertension and urinary renal cancer.[22,23] Using nationally representative data from the Korean National Health Insurance System, 9,746,445 participants without kidney cancer between January 1, 2006 and December 31, 2009 were followed up until December 31, 2017 to obtain data regarding cancer incidence. Participants were categorized, according to blood pressure, as normal (<120/80 mm Hg), elevated (120-129/<80 mm Hg), and hypertensive (≥130/80 mm Hg) with or without antihypertensive medication. Participants with hypertension were at higher risk for kidney cancer than those without hypertension.[172] Another study demonstrted that hypertension is associated with renal cell cancer, and the hypertension resolved after undergoing nephrectomy (removal of the RCC), suggesting that RCCs may cause hypertension.[173]

Introduction to Prostate Cancer

Prostate cancer is the second most common cancer in men worldwide, only second to lung cancer. In 2018, the incidence of new cases of prostate cancers was 211,893 cases (age adjusted rate 107.5/100000 people) and 37,488 people died of this cancer (age adjusted rate 19/100000 people).[34] The current lifetime risk of prostate cancer for men living in the United States is estimated to be approximately one in eight men. The incidence is highly dependent on screening with prostate-specific antigen (PSA), and the number of PSA-driven biopsies, because many of these cancers remain indolent, latent, and occult, and more often than not patients die with the cancer, not from it. Therefore, more intense screening for it will identify more, but not necessary change overall survival rates from prostate cancer. Indeed, as above, the USPSTF recommends PSA testing for prostate cancer screening with low grade, only for "selected patients depending on individual circumstances" (Grade C) for men between the ages of 55-69, while they recommend against screening (Grade D) for men ages >70.[43,44] Prostate cancer has a strong inherited component and men with a family history of prostate cancer on either side of the family, particularly those with a first-degree relative who was diagnosed at age <65 years, are at increased risk for prostate cancer,[174,175] and this is where increased screening is generally recommended. A central argument against routine PSA screening otherwise is that many of these cancers, if left undetected, would never have become clinically meaningful during a man's lifetime.

Unmodifiable risk factors include obviously gender, but also most importantly age. Prostate cancer has the stongest relationship between age and any human cancer. The widespread prevalence of occult prostate cancer in older men and the dramatic increase with age are illustrated by a review of autopsy studies conducted in multiple countries.[176] This autopsy series showed that the incidence of occult prostate cancer increased with age in men (age 20 to 30 years, 2-8%; 31-40 years, 9-31%; 41-50 years, 3-43%; 51-60 years, 5-46%; 61-70 years, 14-70%; 71-80 years, 31-83%; 81-90 years, 40-73%). The variability between reports may reflect differences in pathologic techniques, or geographic differences due to environmental or ethnic factors. Another unmodifiable risk factor is ethnic factors, where prostate cancer is more common in African American men, compared to Caucasion and Hispanic men. The annualized average incidence rates for men in the early 70s per 100,000 people, is approximately 1600, 1000, and 700 for African American men, compared to Caucasion and Hispanic men, respectively.[177] As above, another risk cancer for prostate cancer is inherited predisposition, particularly in family members diagnosed at younger age.

Modifiable risk factors include cigarette smoke, particularly in African Americans.[178] Moreover, data suggest an association of smoking at the time of diagnosis with risk of a prostate cancer recurrence and cancer-related mortality.[179,180] . Other risk factors include obesity,[181,182,183] sedentary lifestyle,[184] infection,[185] and environmental carcinoges including agent orange, chlordecone (insecticide), and bisphenol A estrogen. Hypertension has been found to have a small increased risk of prostate cancer in a meta-analysis (RR 1.08, 95% CI 1.02-1.15, p=0.014).[186] There was a significant heterogeneity among the included studys, and therefore residual confounding are possible. There has been an association of prostate cancer and infertility.[187] An association between ejaculatory frequency and a lower risk of prostate cancer has been suggested.[188,189] Exposure to ultraviolet light, likely increasing vitamin D, and

vitamin D have been associated with a protective effect on the development of prostate cancer.[190,191]

Of all the factors discussed and associated with prostate cancer, increasing age is by far the most important factor.

Introduction to Uterine Cancer

In 2018, the incidence of new cases of uterine cancers (or endometrial cancer) was 58,060 cases (age adjusted rate 27.5/100000 people) and 11,238 people died of this cancer (age adjusted rate 5/100000 people).[34] The incidence peaks between ages 60 and 70 years, but 2 to 5 percent of cases occur before age 40 years. Uterine cancers are broadly classified into two major types that have different clinicopathologic characteristics and risk factors (Type 1, and Type 2).[192] Type 1 neoplasms have low-grade (International Federation of Gynecology and Obstetrics [FIGO] grades 1 and 2) endometrioid histology and comprise the majority (80 percent) of uterine caners. The less common type 2 neoplasms (FIGO grade 3 endometrioid histology and nonendometrioid histologies: serous, clear cell, mixed cell, undifferentiated, carcinosarcoma) are typically not estrogen-sensitive. Risk factors include lower body mass index, non-White race, and older age.

The primary risk factor for type 1 uterine cancer is long-term exposure to increased estrogen levels from an exogenous or endogenous source without adequate opposition by a progestin. Lynch syndrome is a genetic risk factor for several cancers, including uterine cancer. There is an increasing incidence of uterine cancer, associated with increasing prevalence of obesity, decreasing use of menopausal hormone therapy with progestins, increasing prevalence of diabetes, and changes in reproductive behaviors (e.g., increasing prevalence of nulliparity or no children).[193] Patients deemed to be at high risk (eg. Lynch syndrome) for developing uterine cancer have strategies to prevent it, including hysterectomy and/or mitigating as well as their underlying risk factors. Hysterectomy is the most aggressive approach; more conservative approaches include achieving and maintaining a normal body mass index and using progestin-dominant contraceptives. Estrogen-progestin or progestin-only contraceptives are protective factors.

There are no medical societies that list NDMA as a risk factor for genitourinary cancers (including bladder, renal, prostate, and uterine cancers) as a consideration of etiology, nor do any guidelines suggest that treatment of screening/surevillance of genitourinary cancer is changed in any way for patients who might have been exposed to NDMA imuprities in VCDs.

8d. Introduction to Breast Cancer

Globally, breast cancer is the second most frequently diagnosed malignancy just behind lung cancer. In 2018, the incidence of new cases of breast cancers was 254,744 cases (age adjusted rate 127/100000 people) and 16,641 people died of this cancer (age adjusted rate 4/100000 people).[34] The incidence rates are highest in North America, Australia/New Zealand, and in western and northern Europe and lowest in Asia and sub-Saharan Africa. These international differences are likely related to societal changes as a result of industrialization (eg, changes in

fat intake, body weight, age at menarche, and/or lactation, and reproductive patterns such as fewer pregnancies and later age at first birth).

Modifyable risk factors associated with increased incidence of breast cancer in women include alcohol, obesity, sedentary lifestyle, no children, not breastfeeding, birth control, hormonal therpay after menopause, and breast implants (with a rare type of breast cancer). Factors that cannot be modified include female gender, older age, germline (inherited) genetic risk and family history of breast cancer, personal history of breast cancer, ethnicity (higher in African American women), dense breast tissue, benign breast conditions like lipomas and many others, early onset menstruation, late menopause (after age 55), and prior radiation to the chest. There are no medical societies that list NDMA as a risk factor for breast cancer as a consideration of etiology, nor do any guidelines suggest that treatment of screening/surevillance of breast cancer is changed in any way for patients who might have been exposed to NDMA imuprities in VCDs.

As noted above, due to the high incidence of commonality of breast cancer in the United States, routine screening is recommended by the USPSTF starting at age 50 in all women. However, up to 15 percent of women are diagnosed with breast cancer due to the presence of a breast mass that is not detected on mammogram (mammographically occult disease), and another 30 percent present with a breast mass in the interval between mammograms (interval cancers).[194] As noted, patients with known inherited pathogenic gene mutations in BRCA1, BRCA2, or others are recommended to start screening earlier, and also consider prophylactic mastectomies to decrease risk of breast cancer mortality.

There are no medical societies that list NDMA as a risk factor for breast cancers a consideration of etiology, nor do any guidelines suggest that treatment of screening/surevillance of breast cancer is changed in any way for patients who might have been exposed to NDMA imuprities in VCDs.

8e. Introduction to Hematologic (Blood) Cancer

"Hematologic cancer" is a broad term that includes a number of heterogenous malignancies including leukemias, myelomas, and lymphomas. The malignant cells interfere with production of normal blood cells, causing weakness, infection, bleeding, and other symptoms and complications. In 2018, the incidence of new cases of leukemia was 50,174 cases (age adjusted rate 13/100000 people) and 23,503 people died of this cancer (age adjusted rate 6/100000 people). In 2018, the incidence of new cases of myeloma was 26,593 cases (age adjusted rate 7/100000 people) and 12,326 people died of this cancer (age adjusted rate 3/100000 people). In 2018, the incidence of new cases of non-Hodgkin lymphoma was 71,005 cases (age adjusted rate 18/100000 people) and 20,287 people died of this cancer (age adjusted rate 5/100000 people). In 2018, the incidence of new cases of Hodgkin lymphoma was 8,385 cases (age adjusted rate 3/100000 people) and 1,038 people died of this cancer (age adjusted rate <1/100000 people).[34]

Each of the many hematologic neoplasms are relatively rare. Acute myelogenous leukemia (AML) is the most common form of acute leukemia, rapidly growing cancers that originate in

the bone marrow. AML has a median age of diagnosis of approximately 65 years, and the incidence increases with age.[195] AML has been associated with environmental factors (eg, exposure to chemicals, radiation, tobacco, chemotherapy, retroviruses). In rare cases, AML in adults is associated with inherited genetic abnormalities.

Chronic myeloid leukemia (CML; also known as chronic myelocytic, chronic myelogenous, or chronic granulocytic leukemia) is a myeloproliferative neoplasm characterized by the dysregulated production and uncontrolled proliferation of mature and maturing granulocytes with fairly normal differentiation. CML accounts for approximately 15 to 20 percent of leukemias in adults. Exposure to ionizing radiation is the only known risk factor.[196,197] Rare families in which multiple members develop myeloproliferative neoplasms (MPNs), including CML, have been described.[198]

Lymphomas, cancers of the lymphatic system, are very heterogeneous subgroup of cancers, divided broadly into non-Hodgkin (NHL) and Hodgkin (HL) lymphomas. Diffuse large B cell lymphoma (DLBCL) is the most common histologic subtype of NHL accouting for ~25% of NHLs. Incidence increases with age; the median age at presentation is 64 years for patients as a whole. DLBCL is a heterogeneous group of tumors. Familial aggregation of patients with DLBCL and other NHL subtypes has been noted.[199]

Multiple myeloma (MM) is a relatively uncommon cancer accounting for approximately 1 to 2 percent of all cancers and slightly more than 17 percent of hematologic malignancies and is typically characterized by the neoplastic proliferation of plasma cells producing a monoclonal immunoglobulin. The plasma cells proliferate in the bone marrow and can result in extensive skeletal destruction with osteolytic lesions, osteopenia, and/or pathologic fractures. MM is largely a disease of older adults. The median age at diagnosis is 65 to 74 years.[200] The incidence varies by ethnicity; the incidence in African Americans and Black populations is two to three times that in Whites populations in studies from the United States.[201] The risk of MM increases with body mass index.[202] A small fraction of cases are familial.[203]

In summary, hematologic cancers are a very heterogeneous group of disorders, each of which are relatively rare. There are no medical societies that list NDMA as a risk factor for hematologic cancers or for consideration of etiology, nor do any guidelines suggest that treatment of screening/surevillance of hematologic cancer is changed in any way for patients who might have been exposed to NDMA imuprities in VCDs.

8f. Introduction to Cancers Summary

Cancer is common in the United States, accounting for approximately 25% of all deaths annually (1 in 4 people). However, cancer is not a uniform disease, but rather a large group of heterogeneous cancers, even within a cancer type from the same anatomical site. They are heterogeneous in terms of etiology and risk factors, biology, prognosis, treatments, and survival. Common and unifying risk factors across many cancers include those that are not modifiable such as higher age, as well as gender (e.g. prostate in men, breast cancer in women), as well as modifiable risk factors like obesity, smoking, high fat and low fibre diets, and

sedentary lifestyle. Notably, each of those modifiable risk factors for all these types of cancer are also comorbidities commonly observed in hypertensive patients.

In all the cancers reviewed above, there are no medical societies that list NDMA as a risk factor to consider as to the etiology of the cancers nor to counsel to avoid exposure to, nor do any guidelines suggest that treatment or screening/surveillance of any of the cancers should be changed in any way for patients who might have been exposed to NDMA imuprities in VCDs.

9. Valsartan and valsartan containing drugs (VCDs)

9a. Background: Generic medications incorporating valsartan

According to the CDC, nearly half of adults in the United States (108 million, or 45%) have hypertension defined as a systolic blood pressure ≥ 130 mm Hg or a diastolic blood pressure ≥ 80 mm Hg, or are taking medication for hypertension. Valsartan is an angiogtensin II receptor antagonist (ARB) and works as a anti-hypertensive agent by blocking the effects of angiotensin.[204,205] The maximum dose of valsartan is 320 mg per day. It also became available in combination with other anti-hypertensive drugs, such HCT (valsartan and hydrochlorothiazide) or amlodipine.

ARBs in addition to standard anti-hypertensive medical therapy, are generally intended for use in patients with acute myocardial infarction (MI, 'heart attack') who are at high risk of a subsequent cardiovascular event (i.e. those with heart failure, left ventricular ejection fraction ≤40 percent, diabetes, or chronic kidney disease).[206] The addition of an ARB to standard medical therapy (including antiplatelet therapy, beta blocker, and statin) in patients with recent myocardial infarction (MI) improves cardiovascular outcomes.[206] In this scenario, the therapy is recommended indefinitely.

In summary, hypertension is a common illness in the United States and a significant risk factor for the development of cardiovascular disease, the leading cause of mortality. Antihypertensive drugs, including VCDs, are routinely and commonly prescribed to treat hypertension and complications of cardiovascular disease.

9b. VCDs and other ARBs Are Not Associated With an Increased Cancer Risk

On July 2010, FDA communicated its intent to conduct a safety review of ARBs after a published meta-analysis of 5 randomized clinical trials reported a small but statistically significant increase in risk of cancer in patients taking an ARB compared to patients not taking an ARB.[207] To further evaluate the reported link between use of ARBs and cancer, FDA conducted a trial-level meta-analysis of clinical trials in which patients had been randomized to an ARB treatment or a non-ARB treatment, including 31 trials and approximately 156,000 patients, far more than the approximately 62,000 in the previously published analysis.

FDA's more comprehensive meta-analysis did not show an increased risk of cancer in the patients taking an ARB medication as reported on June 2, 2011.[208] The FDA reported "The 31 trials included 84,461 patients randomized to ARBs and 71,355 patients randomized to non-

ARB comparators, with an average follow-up of 39 months. The rate of incident cancer events in the ARB group was 1.82 per 100 patient-years, and the rate in non-ARB comparators was 1.84 per 100 patient-years. The relative risk of incident cancer in patients taking ARBs was 0.99 (95% confidence interval 0.92 to 1.06). The estimate of risk was similar irrespective of the choice of statistical method (random effects or fixed effects), as well as the choice of comparator arm used in the analysis (all comparators, placebo only, active-comparators only)." They also reported that they, "also found no evidence of association between ARBs and cancer-related death (relative risk 1.04, 95% confidence interval 0.96 to 1.13), breast cancer (odds ratio 1.06, 95% confidence interval 0.90 to 1.23), lung cancer (odds ratio 1.07, 95% confidence interval 0.89 to 1.29), or prostate cancer (odds ratio 1.05, 95% confidence interval 0.95 to 1.17)." These findings are consistent with other studies that all suggest no increased risk of cancer related to ARB use.[209,210,211] In short, taking an angiotensin II receptor blocker, such as valsartan, is not associated with an increased risk of cancer.

In contrast, as discussed earlier in the report in the "Introduction to Cancer" and its subsections above, hypertension (the underlying condition for which valsartan and other ARBs are commonly prescribed) is associated with a number of known cancer-related risk factors, and also serves as an independent risk factor for cancer. Such an association of hypertension and cancer would be an example of protopathic bias/reverse causation,[212] where "a pharmaceutical agent is inadvertently prescribed for an early manifestation of a disease that has not yet been diagnostically detected",[212] or in this case, anti-hypertensive medications prescribed for a condition (hypertension, congestive heart failure etc) that is closely associated with cancer-related risk factors (diabetes, obesity, metabolic syndrome) and also a risk factor in and of itself.[23,24,209,213] As such, while taking valsartan does not increase one's risk of any cancer, hypertension and its associated conditions (obesity, smoking, alcohol use, sedentary lifestyle, high fat diet, etc.) do increase an individual's risk for numerous cancers, including the cancers at issue in this litigation. As such, we can expect that cancer incidence in the population of valsartan users will be higher than the incidence of those cancers among the general population. Simply put, correlation does not prove causation.

10. Relevant Background: VCDs with NDMA or other impurities

In June 2018, Zhenjiang Huahai Pharmaceuticals (ZHP), the manufacturer of the active pharmaceutical ingredient (API) for generic valsartan used by some of the Defendant pharmaceutical companies reported that it had detected the presence of a previously undetected impurity — NDMA — in the active pharmaceutical ingredient for valsartan. According to tests of a random selection of API batches performed by ZHP, the levels of NDMA ranged from 3.4 ppm to 120 ppm, with an average of 66.5 ppm.[214]

On July 13, 2018, FDA announced a voluntary recall of several medicines containing valsartan. FDA's announcement stated:

> "The presence of NDMA was unexpected and is thought to be related to changes in the way the active substance was manufactured." The FDA further noted that, "**because valsartan is used in medicines to treat serious medical conditions, patients taking the recalled valsartan-containing medicines**

> **should continue taking their medicine until they have a replacement product**." (emphasis added)

This suggests that the FDA's assessment concluded that the risk of not taking the medication outweighed any potential risks of continuing taking the medication despite the trace impurity.[215] As FDA clarified on July 27, 2018, just two weeks later:

> "NDMA has been found to increase the occurrence of cancer in animal studies. **These animal studies were done using amounts of NDMA much higher than the impurity levels in recalled valsartan batches**. Based on these animal studies, the U.S. Environmental Protection Agency considers NDMA a probable human carcinogen—a chemical that can increase the risk of cancer in humans. NDMA is found in some water supplies and in some foods. Consuming up to 96 nanograms NDMA/day is considered reasonably safe for human ingestion. It is estimated that **over the course of a person's lifetime, consuming this amount [96ng/day or 0.096µg/day] of NDMA would result in less than one additional case of cancer for every 100,000 people. To put this in context, currently one out of every three people in the US will experience cancer in their lifetime**." (emphasis added)[216]

As discussed earlier the current estimate is that cancer accounts for 25% of all deaths in the United states (or 1 in 4 deaths) in 2018. However, the estimate over coming years takes into account the growing rate, and the FDA indicates here that in the future this will be ~33% of all deaths (or 1 in 3 deaths) that are due to cancer. In its announcement on July 27, 2018, FDA went on to say that,

> "the amounts of NDMA found in the recalled batches of valsartan exceeded these acceptable levels. **The agency wanted to put some context around the actual potential risk posed to patients** who used versions of valsartan that may have contained high levels of NDMA. Based on records from the manufacturer of the recalled valsartan, **some levels of the impurity may have been in the valsartan-containing products for as long as four years.** FDA scientists estimate that **if 8,000 people took the highest valsartan dose (320 mg) from the recalled batches daily for the full four years, there may be one additional case of cancer over the lifetimes of these 8,000 people.** This assessment led to FDA's decision to have these batches recalled"

It should be noted again, that there were 436 new cases of cancer in 2018 per 100,000 (or 4.36 cancers/1,000 people per year) in the United States - that is, 436 new cases per 100,000 people (or 4.36/1,000) ***per year***. While this includes all cancers, the alledged cancer types in this litigation include all the most common cancers and others. Moreover, 'over a lifetime' which could be estimated to range for 30-50 years on average for patients taking these medications since most people with hypertension are already above the age of 40, there would be a total of 13,080-21,800 cancers diagnosed per 100,000 people (131-218 cancers per 1,000 people) over these 30-50 years at current incidence rates.

In contrast, the FDA's notification with regard to valsartan drugs estimated an additional 1/8,000 (or 0.125/1000, or 12.5 cancers diagnosed per 100,000 people) lifetime risk, or "70 years" versus 305 total cancers per 1000 people over 70 years at current incidence rates. This is a relatively low increased risk (0.125/1000 on top of 305/1000, which is 0.041% increased relative incidence due to NDMA over baseline incidence), and is derived from the assumption that all patients would take the highest doses of valsartan drugs throughout the full period in which the NDMA impurity had existed and that the impurity had existed at the highest level in each prescription used.

This 'worst case scenario' calculation has many assumptions that most if not all individuals would not meet. Obviously, many valsartan patients were not taking the highest (320mg) dose. Also, some doses tested did not have any level of detectable impurity and patients may have taken valsartan during this period that did not contain any trace amounts of NDMA/NDEA or that contained amounts below the current acceptable limits. As such, it is not reasonable to assume that FDA's 'worst case scenario' estimate of potential NDMA/NDEA exposure would actually apply to any plaintiff in this litigation. FDA stated the same, in January 2019:

> ***"The vast majority of patients exposed to NDMA through ARBs received much smaller amounts of the impurity than this worst-case scenario. Since not all ARBs are affected, it's very likely that a patient taking an ARB for four years would not have always received one of the affected products."*** (emphasis added)"[217]

As set forth below, there is no reliable data which supports any actual increased risk of cancer from valsartan containing the NDMA impurity. Simply, there is significant reason to doubt that ingestion of NDMA at the trace levels detected in valsartan drugs, over the four years in which the impurity existed, would lead to any excess cancer risk. An individual's risk of developing any individual cancer type would be influenced much more significantly by their baseline factors and etiologies.

Further, because even the FDA's "worst case scenario" calculation is of such a low risk as compared against the life-saving value of valsartan to patients, the FDA reminded patients to continue to take valsartan until a replacement could be found. As FDA advised patients on August 30, 2018,

> "Although **the risk to patients taking the affected products is extremely low**, we take matters of pharmaceutical quality very seriously. We took immediate steps to address these findings."
>
> "However, we did not want patients taking valsartan to hear this news and **abruptly stop their medications, possibly suffering serious medical issues**, such as stroke."[218]

FDA's advisory makes clear that the risk of cancer from valsartan containing the NDMA impurity is outweighed by the risks associated with discontinuing valsartan, again reflecting its value as a life-saving and life-prolonging medication. In short, if patients discontinued their ARB treatment, many more would die or suffer serious adverse consequences from cardiac

events than would be at risk for cancer, even under the FDA's own worst-case-scenario estimates.

The risk reduction in carvioascular effects of antihypertensives in general, including VCDs and ARBs, was recently reported in a large meta-analysis, which demonstrated that improved blood pressure led to fewer cardiovascular adverse events — 8.1% with antihypertensives (or more aggressive regimens) vs 8.7% (with placebos or less aggressive regimens), which is a relative risk reduction of ~7%.[216,217] A secondary outcome, all-cause death, however did not show any differences between these groups.

In other words, despite these marginal improvements in terms of decreased cardiovascular events and negligible impact on survival from antihypertensive medications, the FDA indicated that even their worst case scenario for increased cancer risk due to the exposures to NDMA in VCDs were even more miniscule in comparison to the health risks of not taking these blood pressure medications.

FDA also recognized that the valsartan manufacturers had no reason to test for the NDMA impurity previously:

> **"Because it was not anticipated that NDMA would occur at these levels in the manufacturing of the valsartan API, manufacturers would not have been testing for it. They would not have records that help identify this issue during an inspection. So this particular risk would not have been identified on an inspection."**

The impressions that these statements make are first, that NDMA at these trace levels are unlikely to be significant. Second, they indicate that in order to successfully test for a given impurity in API, manufacturers would need to be aware that NDMA could be present in the first place. Third they indicate that even at that point (August 2018), FDA was not entirely sure how NDMA was forming, even after investigating the process in great detail.

On May 2, 2018, FDA posted laboratory test results showing NDMA levels in recalled valsartan products, and the table was most recently updated on 5/2/19 and now includes NDEA level information:[221]

Company	Product (tablets)	Lots Tested	NDMA level (micrograms - mcg/tablet)	NDEA level (micrograms - mcg/tablet)
Aurobindo Pharma Ltd	Amlodipine 10mg/Valsartan 320 mg	VKSA18005-A, VKSA18007-A, VKSA18001-A	Below LOD	0.02-0.09

Aurobindo Pharma Ltd	Valsartan 320mg	VUSD17008-A, VUSD17001-A, VUSD17009-A	Below LOD	0-0.05
Aurobindo Pharma Ltd	Valsartan 320mg/HCT 25mg	HTSB18001-A, HTSB18028-A, HTSB18029-A	Below LOD	0.02-0.19
Hetero Labs Ltd	Valsartan 320mg	VLS18049, VLS18051, VLS18050	0.33-0.44	Below LOD
Mylan Pharmaceutical Inc.	Amlodipine 10mg/Valsartan 320 mg	3079709, 3077618, 3079708	Below LOD	0.04-0.11
Mylan Pharmaceutical Inc.	Amlodipine 10mg/Valsartan 320 mg/HCT 25mg	2008702	Below LOD	0.05
Mylan Pharmaceutical Inc.	Valsartan 320mg	3080009, 3080010, 3079205	Below LOD	0.07-0.16
Mylan Pharmaceutical Inc.	Valsartan 320mg/HCT 25mg	3084886, 3093804, 3084862	Below LOD	0.20-0.38

Prinston Pharmaceutical	Valsartan 320mg	344B18027, 344B18028, 344B18029	15.18-16.30	Below LOD
Prinston Pharmaceutical	Valsartan 320mg/HCTZ 25mg	611B18025, 611B18026, 611B18027	13.18-20.19	Below LOD
Teva Pharmaceutical	Amlodipine 10mg/Valsartan 320 mg	26X053, 26X054, 26X055, 26X051, 26X044, 26X048	Below LOD	0-0.03
Teva Pharmaceutical	Amlodipine 10mg/Valsartan 320 mg/HCT 25mg	22X045, 22X046, 22X047, 22X038, 22X041	Below LOD	0-0.03
Teva Pharmaceuticals	Valsartan 320mg	1240425A, 1247282M	7.92-16.55	Below LOD
Teva Pharmaceuticals	Valsartan 320mg/HCTZ 25mg	1217576M, 1217577M, 1217578M	6.94-10.35	0-0.77
Torrent Pharmaceuticals	Amlodipine 10mg/Valsartan 320 mg/HCTZ 25mg	BBX2E001, BBX2E002, BBX2E003	10.24-11.53	Below LOD
Torrent Pharmaceuticals	Valsartan 320mg	BV48D001, BV48D002	0.56-0.62	1.12-1.22
Torrent Pharmaceuticals	Valsartan 160mg	BV47D001	0.45	1.31

As this table reflects, in many lots of the VCDs at issue, there was no NDMA detected, while in other lots the NDMA levels per tablet were 6.94 to 16.55 ug. Similarly for NDEA, in some lots the levels were below the limits of detection while in others the range was 0-0.03 mcg/tablet.

On April 4, 2019, FDA issued a further statement: "FDA Statement on the agency's list of known nitrosamine-free valsartan and ARB class medicines, as part of agency's ongoing efforts to resolve ongoing safety issue"

> "And while we've concluded through **our risk assessments that the maximum possible exposure to nitrosamines (which are also known environmental contaminants and found in water and foods, including meats, dairy products and vegetables) in ARB medicines appears to be small**, their presence in drug products is not acceptable." (emphasis added)

> "Patients should continue taking their medicine until their pharmacist provides a replacement or their doctor provides an alternative treatment option -- **even if they learn that their ARB medicine is recalled. The risk associated with abruptly discontinuing the use of these important medicines far outweighs the low risk that our scientists estimate to be associated with continuing the medicine until the patient's doctor or pharmacist provides a safe replacement or a different treatment option**. We're closely monitoring the supply of ARBs and will communicate any drug shortages promptly to the public. Today's news, of the certainty and broad number of nitrosamine-free ARB medicines, is another positive step. Health care practitioners should familiarize themselves with alternative medicines that can be used to treat hypertension, heart failure or renal disease in case of shortages.." (emphasis added)[222]

On August 28, 2018, FDA issued a further statement "clarifying the risk and scope of exposure"

> "Clarifying the risk and scope of exposure
>
> As part of our efforts to be transparent regarding impurities in ARBs, we want to make sure patients have a full understanding of how these impurities may affect them. **Notably, we would like to stress that the actual risk to patients is likely much lower than our estimates**, **which reflect a scientific assessment of the highest possible exposure**. We initially estimated that if 8,000 people took the highest valsartan dose (320 mg) containing N-Nitrosodimethylamine (NDMA) from the recalled batches daily for four years, there may be one additional case of cancer over the lifetimes of those 8,000 people**. In reality, the vast majority of patients exposed to NDMA through ARBs received much smaller amounts of the impurity than this worst-case scenario, and, since not all ARBs are affected**, **it's very likely that a patient taking an ARB for four years would not have always received one of the affected products**." (emphasis added)[223]

The impressions that these statements make are first, that NDMA at these trace levels are unlikely to be significant to patients, and that there would be a number of patients thinking they were exposed to lots with impurities, but that many would not have been, and therefore not at any increased risk of any harm.

In the course of its investigation of the nitrosamine inpurity, FDA published what it considered to be acceptable limits of NDMA and NDEA exposure, reflecting the scientific evidence that people routinely are exposed to varying levels of NDMA and NDEA in food, water, air, cosmetics, and through endogenous formation.[222]

Interim Limits for NDMA and NDEA in Angiotensin II Receptor Blockers (ARBs)

Drug	Maximum Daily Dose (mg/day)	Acceptable Intake	Acceptable Intake	Acceptable Intake	Acceptable Intake

		NDMA (ng/day)*	NDMA (ppm)**	NDEA (ng/day)*	NDEA (ppm)**
Valsartan	320	96	0.3	26.5	0.083
Losartan	100	96	0.96	26.5	0.27
Irbesartan	300	96	0.32	26.5	0.088
Azilsartan	80	96	1.2	26.5	0.33
Olmesartan	40	96	2.4	26.5	0.66
Eprosartan	800	96	0.12	26.5	0.033
Candesartan	32	96	3.0	26.5	0.83
Telmisartan	80	96	1.2	26.5	0.33

> "* The acceptable intake is a daily exposure to a compound such as NDMA or NDEA that results in a 1:100,000 cancer risk **after 70 years exposure.** (emphasis added to remind that this is the risk to increase cancer in 1 person per 100,000 over 70 years of continuous exposure at this level)
>
> ** These values are based on a drug's maximum daily dose as reflected in the drug label. For comparison with the levels of NDMA found in some common foods, please see our Aug. 20, 2018, update."

In publishing these "limits", FDA specifically referred the public to context provided by the a table setting forth the amounts of NDMA present in example food items. The table referenced, published on August 20, 2018, states that "NDMA is a known environmental contaminant. For context, it is found in water and foods including meats, dairy products and vegetables." It presented an "Estimated Range of Daily NDMA Consumption for certain foods (Recommended daily food consumption rates based on Dietary Guidelines for Americans 2015-2020):

- Cured meat - 0.004-0.23 micrograms
- Smoked meat - 0.004-1.02 micrograms
- Grilled meat - 0.006-0.13 micrograms
- Bacon - 0.07-0.09 micrograms[222]

This table makes clear that NDMA exposure is a routine part of human life. Indeed, as set forth below, estimates for total dietary NDMA consumption often exceed the FDA's suggested "acceptable intake." Accordingly, to truly assess whether VCDs containing the NDMA impurity pose an increased risk of cancer at the levels tested in VCDs and over the duration

during which the impurity existed, it is critical to look at epidemiologic and other data concerning NDMA.

While I understand that other experts offered in this litigation will provide detailed opinions and a comprehensive review of the epidemiologic data at issue, I have reviewed the reports submitted by Plaintiffs' experts and the studies cited therein, as would be typical in my practice and for others in my field, and I feel compelled to provide commentary on some of the obvious limitations of the data on which they have relied and the ways in which the opinions proffered are not and cannot be supported by the data.

11. Epidemiologic Data Does Not Support Any Increased Risk of Cancer Caused by Ingestion of NDMA at the Levels Detected In Valsartan Containing the NDMA Impurity.

As set forth above, I have been asked to opine on whether there is sufficient data to support the conclusion, advanced by some of the plaintiffs' experts in this litigation, that, to a reasonable degree of medical certainty, ingestion of NDMA at the trace levels detected in some valsartan drugs could have caused the cancers that the plaintiffs have alleged in this litigation. It is my opinion that the data do not support that conclusion.

Any assessment of data concerning whether a particular exposure causes an effect under investigation needs to begin with and place the most weight on epidemiologic data that actually studies the relationship between the exposure (here, valsartan containing the NDMA/NDEA impurity) and the effect (cancer).

There are a few direct examinations of this relationship in the medical literature and my analysis begins with them. Plaintiffs' experts misguidedly focus their attention extensively on less valuable dietary nitrosamine studies and animal studies on nitrosamines which, as I explain below, are only weakly related to the inquiry at issue.

11a. Epidemiologic Data on Valsartan Do Not Support a Causal Association Between Exposure to NDMA in Valsartan and Cancer Risk

There have been two large cohort studies of individuals known to have filled prescriptions for valsartan produced by manufacturers in which the NDMA impurity was identified. Those studies compared individuals who took valsartan known or presumed to contain the NDMA impurity and individuals who took valsartan not believed to contain the impurity; the studies looked specifically at the rates of cancer in each cohort and found no statistically significant differences in cancer incidence among the two groups (with the exception of a possible association with hepatobiliary cancer, in one of the studies, discussed further below). This is the most valuable epidemiologic data that exists on this issue.

In 2018, Dr. Pottegard and his colleagues examined the potential risk of cancer for individuals exposed to valsartan products potentially containing the NDMA impurity compared to individuals who took valsartan products not believed to contain that impurity.[224] The study subjects were identified from the national Danish registry between September 2011 and June 2017. No statistically significant associations were reported between valsartan products potentially containingNDMA and any type of cancer, the primary endpoint (HR 1.09 [0.85-

1.41] with 302 events). In subgroup secondary analyses by cancer type, there was no individual cancer that had a statistically significant association of valsartan products potentially containing the NDMA impurity. This study has strengths including the use of a high quality nationwide registry, therefore limiting selection bias. It also used drug dispensing data rather than prescription data, limiting bias due to non-adherence. The study also appropriately categorized subjects to limit immortal time bias. So while the study was somewhat limited bya relatively short follow-up time (median 4.6 years), this peer-reviewed study, designed to look for any association between valsartan use and cancer, found none — i.e. no association between valsartan containing the NDMA impurity and any cancer. Moreover, comparison of cancer incidence between those patients who were taking valsartan at the study time frame onset (prevalent users) versus those initiating valsartan during the time frame did not show that longer duration of treatment was associated with any higher cancer risk, suggesting that longer term follow up would not increase cancer risk later as opposed to earlier.[224]

In 2021, Dr. Gomm and his colleagues conducted a second but similar study comparing more than 400,000 patients who had taken some valsartan containing the NDMA impurity against 371,688 patients who had never been exposed to valsartan containing the NDMA impurity.[225] The strength of this study is that all patients evaluated were taking valsartan. Also, all subjects had filled at lease one prescription for valsartan during the period 2012 to 2017.[1] Whether a subject was exposed to potentially NDMA-containing valsartan was determined by detailed information from the manufacturers reflecting which batches of valsartan were produced by manufacturers whose product(s) were shown to contain the impurity (i.e. ZHP). Given the very large size of the study population, this study was well-powered to detect any association between NDMA-containing valsartan and increased cancer risk. However, no such association was observed overall (adjusted HR 1.01, 95% CI [0.99-1.03]. In other words, taking NDMA-containing the valsartan impurity was not associated with any increased risk in overall cancer or with any specific cancer. The analysis of individual cancer types, did show a slight statistically significant association, but not causation, between potentially NDMA-containing valsartan and liver cancer (adjusted HR 1.16 [1.03; 1.31], p = 0.017) but not for any other cancer evaluated (bladder, breast, colorectal, kidney, lung, melanoma, pancreas, prostate, nor uterine cancers). Importantly, there was no dose-dependent effect on the risk of liver cancer found for higher exposure to potentially NDMA-containing valsartan. Long term use (3-year) was not statistically significantly associated with liver cancer either. The authors conclude that their data is consistent with the Danish cohort, and much larger. However, the primary difference in the two studies of the findings of an association between NDMA-containing vasartan in liver cancer is notable that there were no cases of liver cancer detected at all mong persons who had received potentially NDMA-containing valsartan in the Danish study. With multiple testing that has been conducted between the two studies, including for each of the various cancers, there is potential that a positive finding here in Gomm et al is due to mere chance, and further analysis is warranted to derive firm conclusions. Also, a limitation in these observational studies is that without randomization, despite attempt at adjustment of potential influencing factors, residual confounding cannot be entirely excluded.

[1] Notably, by examining all individuals who filled valsartan prescriptions, this study also more closely models the real world exposure and experience of sartan users to the NDMA impurity, as opposed to FDA's "worst case scenario" analysis outlined above.

While each of these studies notes the obvious limitation of a somewhat shortened follow-up period, that period actually is more closely reflective of the plaintiffs in this litigation who claim their cancers similarly developed in a very short time period following their exposure to valsartan containing the NDMA impurity. Specifically, Pottegard et al. and Gomm et al. note that their studies were limited by the short follow-up time between the potential exposures and the assessment of cancer incidence (roughly 0-6 years, depending on the individual's exposure period), with median person-times follow up of 4.6 years (interquartile range 2.0-5.5 years) in Pottegard et al, and 3.25 years (interquartile range 2–4.75 years) in Gomm et al. But, the Plaintiffs in this litigation also claim to have been exposed to NDMA-containing valsartan and to have been diagnosed with cancer in a similarly short period after the exposure. As such, the Gomm and Pottegard studies are actually more closely analogous to the question at hand: whether the level and duration of potential exposure to NDMA from valsartan could have caused the cancers alleged in the short time period during which plaintiffs assert their diagnoses. The data from Gomm and Pottegard do not support that hypothesis.

In short, it is my opinion that the available epidemiological data does not support the hypothesis that exposure to NDMA-containing valsartan causes any excess cancer risk.

11b. Studies on NDMA in Diet and Enviroment Do Not Support an Association between Orally-Ingested NDMA and the Cancers Alleged Here.

Of significantly less relevance to the present inquiry are the plethora of studies — relied upon heavily by plaintiffs' experts — which purport to examine a potential association between dietary nitrosamines and/or nitrosamine precusors (nitrite and nitrate) and the risk(s) of various cancers. For a number of reasons I will discuss throughout this section, those studies present flawed bases to draw conclusions about whether NDMA/NDEA-containing valsartan/VCDs could cause any of the cancers alleged in this litigation.

NDMA is one substance in a class of substances known as N-nitrosamines (or N-nitroso compounds). NDMA and/or nitrosamines are fairly ubiquitous chemicals found preformed in drinking water and some foods, in certain cosemtic and pharmaceutical products and through occupational exposures in certain industrial settings. As such, humans are exposed to exogenous (formed outside the body) nitrosamines such as NDMA every day in their diet and environment. Importantly, NDMA and other nitrosamines can also be formed endogenously (inside the body) by chemical reactions during the digestion of food containing nitrosamine precursors, such as nitrite and nitrate.[226,227] Because humans are exposed to nitrosamines both endogenously and exogensouly, it is not possible to precisely and accurately measure the amount of nitrosamines or NDMA to which any one individual may be exposed on a daily basis.

Many studies have attempted to explore the effect of dietary (i.e. exogenous) nitrosamine consumption on cancer risk, but the results have been mixed and inconclusive. The studies I have reviewed regarding NDMA/nitrosamines and cancer, which have examined NDMA exposure in a variety of these kinds of exposures, do not show, through consistent, reliable data that NDMA presents an increased risk of cancer to humans.

For example, Dr. Choi and his colleagues conducted a cohort study which found a positive association between consumption of *precursors* of n-nitroso compounds and gastric cancer, based on a questionaire of dietary history and estimated levels of n-nitroso compounds in the foods surveyed.[228] The highest risk correlation was with consumption of smoked meats and fish; dietary NDMA was not measured. On the other hand, Chyou, et al., conducted a similar dietary history-based cohort study and found no association between dietary processed meats, dried fish and pickled vegetables and gastric cancer.[229] Likewise, Dr. Jakszyn and colleagues conducted a series of studies examining a hypothetical link between dietary n-nitroso compounds and gastric cancer, bladder cancer, and prostate cancer.[226] They did not find a positive association. In contrast, Dr. Keszei and colleagues conducted a study finding positive association between dietary NOCs and esophageal and other gastric cancers.[227]

As noted above, each of these studies is inherently limited in its utility, because it is based on estimated levels of nitrosamines or even nitrosamine precursors in diet; such a study design is obviously much more attenuated from the instant question of whether NDMA in valsartan/VCDs causes cancer than the direct epidemiological studies I describe above.

One of the biggest impediments in the reliability of this data is the question of how to measure accurately the amount of NDMA/nitrosamines that any individual or population might be exposed to. For example, with regard to dietary exposures, most studies try to obtain this information through "food-frequency questionnaires." These devices are recognized as being inprecise if not unreliable, in that they depend on study participants recalling accurately which foods they consumed and the quantify of such foods, particularly those foods that are considered potential sources of NDMA.[230,231]

Even if study subjects in a nutritional epidemiologic study recall this kind of information accurately, how much NDMA might be in any particular food product, is usually not precisely known. These studies rely on published literature or databases which are not necessarily reliable or accurate. As one study noted: "It is difficult, however, to estimate the N-nitrosodimethylamine intake of individuals based on questionnaire and published data on N-nitrosodimethylamine contents of food. The nitrosamine contents of food vary across countries and over time, because of changes in methods of food processing, and available data are limited for some food items… food-frequency questionnaires are prone to the misclassification of dietary intake…"[227]

Importantly, however, some studies have attempted to estimate the total dietary intake of NDMA and/or N-nitrosamines. One researcher estimated that his study population consumed .123 µg/day of NDMA daily, from food and beer.[232] Another calculated the 75th percentile intake of NDMA among study participants at .51 µg/day; a third calculated the highest consumption group as averaging .179 µg/day.[233,234] These results reflect the significant variability in estimating NDMA in diet; they also show that adults may consume far more NDMA through diet alone than the amount FDA has deemed a safe daily exposure.

Notably, that figure does not account for any endogenously formed NDMA to which we are exposed. Some studies have estimated that endogeously formed NDMA/nitrosamines account for between 45%-75% of total exposure; some estimates have been even higher.[226,235] Dr.

Jakszyn and colleagues concluded that endogenous exposure (i.e. exposure to chemicals synthesized in the body) is "probably the major contributor to the overall burden of human exposure to NOCs [nitroso compounds]." They estimated that study participants were exposed to 93 µg/day on average from endogenously formed NOCs, as compared against less than 1 µg/day from exogenous sources.[226] Fristachi et al., while noting the difficulty of estimating the amounts of endogenously formed NDMA, calculated a level of .37 µg per gram of nitrate/nitrite rich foods consumed.[235] They also noted a series of studies (Groenen, 1980; Sen, 1985; Krul 2004) which reported endogenous formation of NDMA up to 44 µg *per portion* of amine-rich food (e.g. cheeses/dairy, meat/fish). Similarly, Hrudey et al. (2013) analyzed NDMA levels blood samples, levels of the DNA adduct caused by NDMA (O^6-methylguanine) and urinary excretion of NDMA and estimated endogenous NDMA formation between 4 µg/kg/day and 220 µg/kg/day. Under those estimates, a 100kg person would be exposed to between 400 and 22,000 µg of endogenously-formed NDMA daily.[236]

Those studies' estimates suggest that, even under an FDA's "worst case scenario" model of the highest daily exposure possible for the longest time possible of NDMA-containing valsartan, humans are exposed to far more endogenously-formed NDMA. Clearly, many people are exposed to well over the FDA's recommended limit of NDMA on a daily basis, throughout the majority of their lives.

Confounding is another concern that permeates many of these dietary nitrosamine studies. For example, in De Stefani 1998, the study investigators reported a statistically significant association between dietary NDMA and gastric cancer. However, in a follow-up study in the same population but subsequent years (De Stefani 2001), the authors repeated the analysis and found the association was no longer significant when adjusting for additional confounding factors -- total energy intake and intake of proteins and total fat -- which had not been considered in the earlier study. Similarly, Goodman, et al. conducted a study of high fat.[237] Dr. Goodman and his colleagues concluded that high dietary nitrosamine intake is associated with an increased risk for lung cancer; but, the study authors conceded that the association was strongest in men who were heavy smokers, which is clearly a significant confounder. Confounding in nutritional epidemiology is particularly a problem given the number of dietary components in each food item and the diet in general.

Multiple comparisons is another reason that significant associations that really occur by chance alone rather than a true association can compromise the results of studies examining potential dietary risk factors.[238]

Overall, the findings on dietary NDMA and cancer risk are mixed – some studies report a statistically significant association (typically in the group with the highest exposure), while other studies do not. Most of the statistically significant findings are reported in case-control studies and have not been sufficiently replicated in cohort studies. Prospective cohort studies are considered superior to case-control studies in nutritional epidemiology.

There are many limitations to these studies and in general, bias, confounding, and chance cannot be ruled out as likely explanations for the findings.

11c. Studies of Occupational Exposures to NDMA Do Not Support an Association between Orally-Ingested NDMA and the Cancers Alleged Here

Plaintiffs' experts (in particular Dr. Etminan) rely heavily on one study concerning NDMA exposures in an industrial setting. Specifically, Hidajat, et al. (2019) examined NDMA exposure in the UK rubber industry and reported statistically significant increased risks between NDMA and mortality from all cancers combined, bladder, brain, esophagus, leukemia, liver, lung, multiple myeloma, non-Hodgkin's lymphoma, pancreas, prostate, and stomach cancers. Laryngeal cancer mortality was the only cancer with non-statistically significant association.[239]

This study, however, had numerous limitations and confounders, many of which Dr. Etminan uses as the bases for his own criticms of other studies cited in this report. Among other things, Hidjat et al. noted that rubber industry workers are exposed to numerous carcinogens, including N-nitrosamines, rubber (process) dust, rubber fumes, polycyclic aromatic hydrocarbons including phthalates, aromatic amines including β-naphthylamine and solvents including benzene; as they state, "disentangling exposure-response associations between specific suspected carcinogens and cancer risk in this industry remains difficult." Critically, all the exposure considered in this study was by inhalation. That different route of exposure implicates different metabolic pathways, different tissue exposures, and other factors. As a result, any results of a study addressing inhaled NDMA or other compounds is of limited utility in answering the question whether *orally ingested* NDMA could cause the cancers plaintiffs have alleged here. Moreover, the Hidjat study used estimations of NDMA exposure based on job title and air quality measurements associated with those job titles, while also assuming study participants remained in the same position throughout their careers. That is a significant and, in my view, implausible assumption and makes the estimations inherently questionable. Finally, the Hidjat study made no effort to control for smoking history. Obviously, tobacco smoking is one of the most-studied carcinogenic exposures and is known to cause many of the cancers at issue here. Presumably the subjects in the Hidjat study — manufacturing employees in Britain beginning in the 1970s — have significant exposures to tobacco smoke, confounding all of the study's findings.[239]

Other occupational studies considered nitrosamines as a group. In a study of the German rubber industry, Straif 2000, reported on nitrosamines as a group (while noting that NDMA and NMOR, another nitrosamine were found in the highest concentations) and found a statistically significant increased risks between nitrosamines and mortality from all cancers combined, lip/oral cavity/pharynx cancers combined, and esophageal cancer.[240] Additional studies have reported on occupational exposure to nitrosamines (without any specific mention of NDMA) and cancer incidence or cancer mortality. No association was found for occupational exposure to nitrosamines and incidence of pancreatic cancer[241], stomach cancer[238, 242] or stomach cancer mortality.[243] Cocco 1998 found no association between occupational exposure to nitrosamines and gastric cardia cancer mortality. A follow-up study using the same methods[244] reported an association (unadjusted) between occupational exposure to nitrosamines and gastric cancer, although the association lost significance with further adjustment of confounders.

In sum, as with the dietary NDMA studies, these studies also suffer from multiple limitations, particularly with regard to the issues in this case. NDMA (or nitrosamine) exposure in an industrial or occupational setting is by predominantly by inhalation rather than by ingestion. In addition, most studies evaluated nitrosamines as a group rather than NDMA specifically and evaluated cancer mortality rather than cancer incidence. And, like the dietary NDMA studies, these study authors make may assumptions to estimate exposure levels which may or may not be accurate. Moreover, the study authors are unable to eliminate confounding as an issue, since in many of the reports the study authors did not adjust for other occupational exposures, for smoking, or for other factors. As such, much less weight can be given to these studies than to direct epidemiological evidence that looked at NDMA-containing valsartan. I give little weight to this evidence and could not rely on it to render any opinions about carcinogenesis that were offered to a reasonable degree of medical certainty.

11d. NDMA Animal Studies

In the expert reports I have reviewed from the plaintiffs' experts, there are several references to animal studies on the carcinogenic potential of NDMA. *E.g.,* Etminan Report at p. 22; Lagana Report at p.32; Panigrahy report at p. 35. While those studies, broadly speaking, have demonstrated that NDMA is carcinogenic to several animal species, they do not serve as a meaningful basis to infer carcinogenecity in humans, particularly at the dose levels in this litigation.

Plaintiffs' experts focus extensively on the study by Peto, et al. (1991) concerning NDMA's carcinogenesis in rats.[245,246] In that study, the researchers administered doses up to 840 µg/kg/day – doses approximately 8,750x the .096 µg limit established by FDA. While the authors concluded that NDMA was carcinogenic to the rats and observed a dose-response relationship, they found lifetime liver cancer incidence above the background rate in the control group rats only at doses above 0.3 ppm. Expressed in micrograms, that dose equates to 15 µg/kg/day. For a 100kg human, that would mean 1,500 µg of NDMA, daily, or more than 75 times the amount of NDMA found in any valsartan product, daily for a lifetime. The significantly higher doses used in the Peto et al. study demonstrates why it is inherently unreliable to extrapolate that data to human carcinogenesis.

Other studies, also directly address the limited utility of the Peto et al. data when one attempts to extrapolate it to human carcinogenecity. As one study put it: "Extrapolation of rodent carcinogenesis data to man is particularly difficult because of known species differences in metabolic pathways (both activation and detoxification), involving potentially carcinogenic chemicals."[247]

On the other hand, while animal studies are of limited utility in extrapolating data to draw firm conclusions about human carcinogenesis, none of the animal studies relied upon by Plaintiffs' experts demonstrates that exposure to the levels of NDMA demonstrated to exist in certain valsartan medications would be capable of causing cancer when administered over the brief period that the impurity existed in those medications.

Indeed, animal studies on the carcinogenecity of a broad range of nitrosamines in nonhuman primates have reached precisely the opposite conclusion. Adamson, et al., studied nitrosamine carcinogenesis in non-human primates, because those animals "may provide a more suitable model for the study of potential carcinogens, particularly those requiring metabolic activation." It is well known that NDMA requires metabolization by a specific cytochrome enzyme that only exists in certain human tissues. Studying the more closely analogous monkeys, Adamson et al. stated: "The nitroso compounds as a class appear to be potent carcinogens in nonhuman primates; all but one of these compounds (***N-nitrosodimethylamine***) have induced tumors in monkeys… four of the six monkeys treated with bimonthly intraperitoneal (ip) injections of NDMA (10 mg/kg) have been necropsied, and none have developed tumors." In other words, in a direct study of NDMA's carcinogenicity in monkeys, injections of ***10 mg/kg*** of NDMA — a level far, far, above that demonstrated to exist in valsartan — failed to cause tumorigenesis.[247]

In those same studies, the "apparent cumulative carcinogenic dose" of NDEA required to induce cancer was 1.4 grams. As set forth above, the highest measured level of NDEA in any valsartan medication was 1.3µg (Torrent – 160mg). In other words, Adamson et al. found that no dose of NDMA induced cancer in monkeys and that a cumulative dose of NDEA more than one million times that present in any valsartan pill was the carcinogenic dose.

The authors also noted that the dose response in monkeys was not linear: "The tumors developing in the six animals receiving the 5-mg/kg dose required a latent period of 65 months, a figure that shows a marked deviation from the value (42 months) expected if the relationship between dose and latent period is indeed linear." *Id*.

Similarly, Takayama et al. studied chemical carcinogenesis in non-human primates and found that, when 7 monkeys were treated with 7.25mg/kg of NDMA daily (for a cumulative dose of 7 grams), none died of malignant tumors.[248]

Berger, et al. studied the carcinogenicity in rats of administration of combinations of nitrosamines, including, relevantly, administration of .1mg/kg of NDEA. Among other things, the authors noted that esophageal cancer incidence fell from 26% to not detectable levels, when the dose of NDEA was reduced from .1mg/kg to .032 mg/kg.[249] Noting that this result differed from the results obtained by Peto et al., the authors hypothesized that differences in the rat species used between the two studies might account for these differences in dose-response relationship. Such a hypothesis underscores the limited utility of linear extrapolation from rats to humans.

Taken together, animal studies that have evaluated the carcinogenicity of NDMA depend on the species studied, doses administered and the duration of exposure. While one rat study concluded that NDMA was carcinogenic and demonstrated a dose response relationship, this was at exceedingly high doses far higher than the limit established by the FDA. Another rat study with a different rat species did not find such relationships. In a more representative species, non-human primates, studies failed to demonstrate NDMA to be carcinogenic even at doses far higher than the trace levels found in VCDs, and also found a non linear dose response

relationship with NDEA. As such, the totality of the animal data, for which I put more emphasis on non-human primate models, suggest the trace levels found in VDCs are not carcinogenic.

12. Summary of Epidemiological, Diet, and Toxicologic Data and Conclusion

It is my opinion, to a reasonable degree of medical and scientific certainty that, considered together, the available epidemiological data, the dietary studies, and the animal studies do not support the hypothesis that exposure to NDMA and/or NDEA-containing valsartan at the levels observed in those drugs and over the duration that those impurities were understood to exist could cause any excess cancer risk (including, specifically, esophageal, gastric, pancreatic, liver and colorectal/intestinal, lung, pharyngeal cancers, bladder, kidney, prostate, uterine, breast, nor hematologic (blood) cancers). Indeed, there is no reliable scientific data that supports the such a hypothesis — i.e. that exposure to valsartan/VCDs containing an NDMA and/or NDEA impurity at the levels observed causes any increased cancer risk. The other risk factors associated with those cancers are many and (along with the natural process of aging) are much more likely to have played a role in the development of any particular plaintiff's cancer than exposure to trace amounts of NDMA and/or NDEA in valsartan/VCDs.

It is likewise my opinion, to a reasonable degree of medical and scientific certainty, that there is no medically justifiable reason to require extra or early cancer screening or enhanced medical monitoring for patients believed to have been exposed to the trace amounts of NDMA and/or NDEA understood to exist in certain batches of valsartan drugs. These opinions are based on based on my training and experience and review of materials and literature, including but not limited to those listed on Exhibit B.

I reserve the right to modify this report and my opinions herein as additional information is provided to me, including but not limited to additional records and the depositions of Plaintiff's experts which are ongoing. I further reserve the right to use at trial any exhibits as a summary or in support of all of my opinions including: (1) any of the materials, or excerpts identified in this report and attachments, including the materials considered list; (2) excerpts from scientific articles or learned treatises; (3) demonstrative models; (4) exhibits used by Plaintiffs' experts, or other witnesses; (5) any exhibit used in or identified at any deposition taken in this litigation. If further data becomes available, I will be happy to review it and consider whether to modify any portion of these opinions.

Best Regards,

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Dated: August 27, 2021

Daniel Catenacci, M.D.

CATENACCI

EXHIBIT A

DANIEL VIRGIL THOMAS CATENACCI, M.D. March, 2021

PERSONAL

Office Address:
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Chicago, IL, 60637
Office (773) 702-7596

Place of Birth: Sarnia, Ontario, Canada
Citizenship: Canadian, U.S. Permanent Resident
E-mail: dcatenac@medicine.bsd.uchicago.edu

EDUCATION:

1995-1999 **Honors Bachelor of Science, BSc.** University of Waterloo, Waterloo, Ontario, Canada.
1999-2003 **Doctor of Medicine, MD.** Wayne State University, Detroit, Michigan.
2011-2014 **Master of Science in Health Studies, MSc** University of Chicago, Chicago, Illinois. Biostatistics, Clinical & Translational Investigation.

POSTDOCTORAL TRAINING:

2003-2006 **Internal Medicine Intern/Resident**
UCLA Medical Center, Los Angeles, California

2006-2007 **Clinical Fellow, Medical Oncology/Hematology**
University of Chicago Medical Center, Chicago, Illinois.

2007-2010 **GI Translational Research Fellow, Digestive Malignancies Laboratory**
PI: Ravi Salgia. University of Chicago Medical Center, Chicago, Illinois.

POSTDOCTORAL EDUCATIONAL WORKSHOPS:

2007 **AACR "Molecular Biology in Clinical Oncology" Workshop**
Given Institute of the University of Colorado, Aspen, Colorado. July 1-7

2007-2008 **Clinical Research Training Program,**
Essentials of Patient Oriented Research (EPOR I)
University of Chicago Medical Center, Chicago, Ilinois. **Fall & Winter**

2008 **Summer Workshops in Molecular Biology, New England Biolabs**
Smith College, Clark Science Center, Northampton, MA. July 6-19.

2008 **ECCO-AACR-ASCO "Methods in Clinical Cancer Research"**
Flims, Switzerland, June 21-27.

2017 **AAI "Advanced Course in Immunology"** Boston, MA. July 23-28.

ACADEMIC APPOINTMENTS

2010-2012 Instructor, Department of Medicine, Section of Hematology/Oncology, University of Chicago, IL
2010- Member, Comprehensive Cancer Research Center, University of Chicago, IL
2012-2018 Assistant Professor, Department of Medicine, Hematology/Oncology, University of Chicago, IL
2016-2018 Associate Director, Gastrointestinal Oncology Program
2018- Director, Interdisciplinary Gastrointestinal Oncology Program
2018- Assistant Director, Translational Research, Comprehensive Cancer Center
2019- Associate Professor, Department of Medicine, Hematology/Oncology, University of Chicago, IL

HOSPITAL APPOINTMENTS

2010- Attending Physician. University of Chicago Medical Center, Chicago, IL.

LICENSURE AND CERTIFICATION:

Licensed to practice medicine:

05/2005-2009 California: #A91242
07/2006- Illinois: #036-115556

American Board of Internal Medicine:

2006-2016 Internal Medicine
2009-2029 Medical Oncology (Hematology: board eligible)

PROFESSIONAL MEMBERSHIPS and ACTIVITIES:

1999-2003 American Medical Association
2003-2004 American College of Physicians
2002- The Pharos, Alpha Omega Alpha AΩA quarterly
2005- Medical Council of Canada
2006- American Society of Clinical Oncology, Associate Member
2006- American Society of Hematology, Associate Member
2007- American Association for Cancer Research, Associate Member
2010- Associate Investigator Pharmacogenomics and Experimental Therapeutics
2010- University of Chicago Comprehensive Cancer Center Member
2013- American Gastroenterological Association, Associate Member
2015- Overseas Fellow of the Royal Society of Medicine, United Kingdom
2016- European Society of Medical Oncology, Associate Member

HONORS AND AWARDS:

1995-1999 University of Waterloo, Waterloo, Ontario, Canada**,** (Undergraduate)**:**

- Dean's Honors List, Undergraduate Year I to Year IV.
- Nominated for the Governor General's Silver Medal and Alumni Gold Medal for highest academic standing in Faculty of Science, 1999
- Recipient of Sony of Canada Science Scholarship for highest academic standing, Faculty of Science, University of Waterloo, 1998

1999-2003 Wayne State University School of Medicine, Michigan (Medical School),:

- Honors with Highest Distinction (*Summa Cum Laude*), Years I to IV.
- *Alpha Omega Alpha* AΩA Honor Medical Society, Inducted Yr II, 2001

1999-2003 Harvard Medical School/Harvard Institute of Medicine (Medical School):

- William F. von Liebig Summer Research Fellowship, Summer, 2000

2003-2006 UCLA Medical Center (Residency):

- Distinguished Teacher Award for UCLA Interns and Medical Students, 2004-2006

2006-2010 University of Chicago Medical Center (Fellowship):

- ASCO 2009 Young Investigator Award (YIA), 07/2009-06/2010.
- Amgen Hematology & Oncology Fellowship Grant Support Program, 04/2008-03/2009

2010-2012 University of Chicago Medical Center (Instructor):

- Cancer Research Foundation Young Investigator Award (CRF YIA). 10/2010-09/2011.
- K-12 Scholar. Paul Calabresi Career Development in Clinical Oncology. 10/2010-09/2013.
- NCI/CTEP Career Development LOI Awarded – A Randomized Discontinuation Trial of OSI-906 in metastatic Colorectal Cancer After Two or More Lines of Prior Therapy 10/29/2010.

2012-2018 University of Chicago Medical Center (Assistant Professor):

- ALLIANCE for Clinical Trials in Oncology Foundation Young Investigator Award 07/2012-06/2013
- Esophago-Gastric NCI Task Force, ALLIANCE New Investigator (06/2012-11/30/17)
- Best Abstract and Oral Presentation at the 5th Annual WIN (Worldwide Innovative Networking in Personalized Cancer Medicine) Symposium. July 7-10, 2013. Paris, France.
    - Towards personalized treatment for gastroesophageal adenocarcinoma: strategies to address inter- and intra- patient tumor heterogeneity: PANGEA
- Best Abstract Translational Research Faculty Category Annual Janet Rowley Research Day University of Chicago, March 4, 2014 PANGEA Clinical Trial Design and Pilot results.
- K23 Scholar Awarded 9/2014-8/2017.
- Named on the "Chicago's Top Cancer Doctors' List. December, 2016
- Tree of Life Medical Award. Debbie's Dream Foundation for Stomach Cancer. April, 2018

2019- University of Chicago Medical Center (Associate Professor):

CLINICAL

I am an adult Medical Oncologist with sub-specialization in Gastrointestinal Cancers, with focus on upper GI cancers, and special interest in Esophagogastric adenocarcinoma and Cholangiocarcinoma/Gallbladder cancer.

2010- GI Oncology Clinic (1 day/week, 12 months/year, **30% effort**)
2010- Inpatient Service - Chemotherapy service, Housestaff Supportive Oncology (4 weeks/year, **10% effort**)

SCHOLARSHIP:
BIBLIOGRAPHY:
***Peer Reviewed Articles*:**

Original Articles

1. Zhang W, **Catenacci DVT,** Duan S, Ratain MJ. A Survey of the Population Genetic Variation in the Human Kinome. *J of Hum Genet.* Aug;54(8):488-92. 2009. PMID 19644514.
2. **Catenacci DVT,** Cervantes G, Yala S, Nelson EA, El-Hassani E, Kanteti R, El Dinali M, Hasina R, Brägelmann J, Seiwert T, Sanicola M, Henderson L, Grushko T, Olopade O, Karrison T, Bang YJ, Kim WH, Tretiakova M, Vokes EE, Frank DA, Kindler HL, Huet H, Salgia R. RON (*MST1R*) is a novel prognostic marker and therapeutic target for gastroesophageal adenocarcinoma. *Cancer Biol Ther.* 12:1, 1-38, July 1, 2011. PMID 21543897. **Featured Article**.
3. **Catenacci DVT**, Henderson L, Xiao SY, Priti Hegde, Premal Patel, Robert L. Yauch, Peterson A, Salgia R. Durable complete response of gastric cancer with anti-MET therapy followed by resistance at recurrence. *Cancer Discov*. 2011 Dec 1;1(7):573-579.PMID: 22389872.
4. Kanteti R, Krishnaswamy S, **Catenacci DVT**, Cervantes G, Henderson L, Tan Y, El-Hassani E, Husain AN, Tretiakova M, Huet R, Salgia R. Differential Expression of RON in Small and Non–Small Cell Lung Cancers. Epub May24 *Genes Chromosomes & Cancer 2012.* PMID 22585712.
5. Shah MA, Wainberg ZA, **Catenacci DVT**, Hochster HS, Ford J, Kunz P, Lee FC, Kallender H, Cecchi F, Rabe DC, Keer H, Martin AM, Liu Y, Gagnon R, Bonate P, Liu L, Gilmer T, Bottaro DP. Phase II Study Evaluating 2 Dosing Schedules of Oral Foretinib (GSK1363089) in patients with Advanced or Metastatic Gastric Cancer. *PLoS One*. 2013;8(3):e54014. PMID:23516391
6. Geynisman DM, Zha Y, Kunnavakkam R, Aklilu D, **Catenacci DVT**, Polite BN, Rosenbaum A, Namakydoust A, Karrison T, Gajewski TF, Kindler HL. A randomized pilot phase I study of modified Carcinoembryonic antigen (CEA) peptide (CAP1-6D)/Montanide/GM-CSF-vaccine (CEA-vac) in patients (pts) with pancreatic adenocarcinoma (PC). *Journal for ImmunoTherapy of Cancer* 2013, **1**:8. PMID pending
7. Ross JS, Wang K, Gay L, Al-Rohil R, Rand JV, Jones DM, Lee H, Sheehan CE, Otto GA, Palmer G, Yelensky R, Lipson D, Morosini D, Hawryluk M, **Catenacci DVT,** Miller VA, C Chaitanya, Stephens PJ.New routes to targeted therapy of intrahepatic cholangiocarcinomas revealed by Next Generation Sequencing. *Oncologist* 2014 Feb 21. PMID 24563076.
8. Salgia R, Patel P, Bothos J, Yu W, Bai S, **Catenacci DVT**, Peterson A, Ratain M, Polite B, Mehnert J, Moss R. Phase I dose-escalation study of onartuzumab as a single agent and in combination with bevacizumab in patients with advanced solid malignancies. Clin Cancer Res. 2014 Feb 27. PMID:24493831.
9. **Catenacci DVT**, Liao WL, Thyparambil S, Henderson L, , Peng Xu, Rambo B, L Zhao, Hart J, Xiao SY, Bengali K, Uzzell J, Dafler M, Krizman D, Cecchi F, Bottaro D, T Karrison, Veenstra TD, Hembrough T, Burrows J. Absolute Quantitation of c-Met using Mass Spectrometry for Clinical Application: Assay Precision, Stability, and Correlation with *MET* gene amplification in FFPE Tumor Tissue. *PLoS One*. 2014 Jul 1;9(7):e100586. PMID:24983965.
10. **Catenacci DVT,** Amico A, Nielsen S, Geynisman D, Carey GB, Gulden C, Fackenthal J, Kindler HK, Olopade F. Tumor Genome Includes Germline Genome - Are We Ready For Surprises? *International Journal of Cancer 2014 August 2014.* PMID 25123297.
11. **Catenacci DVT**. Next-generation clinical trials: Novel strategies to address the challenge of tumor molecular heterogeneity. For: Molecular Oncology Special Edition on “Innovative clinical trials for development of personalized cancer medicine”. *Molecular Oncology October, 2014.* PMID 25557400
12. Ali SM, Sanford EM, Klempner SJ, Rubinson DA, Wang K, Palma NA, Chmielecki J, Yelensky R, Palmer GA, Morosini D, Lipson D, **Catenacci DVT**, Braiteh F, Erlich R, Stephens PJ, Ross JS, Ou SH, Miller VA. Prospective Comprehensive Genomic Profiling of Advanced Gastric Carcinoma Cases Reveals Frequent Clinically Relevant Genomic Alterations and New Routes for Targeted Therapies. *Oncologist.* 2015 Apr 16. PMID 25882375

13. **Catenacci DVT**, Chapman CG, Xu P, Koons A, Konda V, Siddiqui U, Waxman I**.** Acquisition of Portal Vein Circulating Tumor Cells in Pancreatobiliary Cancers by EUS Guided Portal Vein Sampling. *Gastroenterology* doi: 10.1053/j.gastro.2015.08.050. [Epub ahead of print] PMID: 26341722

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15. **Catenacci DVT**, Bahary N, Edelman M, Nattam S, Brockstein B, Sparano J, Kozloff M, Cohen D, Stiff P, Sleckman B, Thomas S, Lenz H, Henderson L, Vannier M, Karrison T, Stadler WM, Kindler HL. Final Analysis of a Phase Ib/Randomized Phase 2 Trial of Gemcitabine plus Placebo or Vismododib (GDC-0449), a Hedgehog Pathway Inhibitor, in Patients with Metastatic Pancreatic Cancer. *J Clin Oncol 2015 2015 Nov 2.* [Epub ahead of print]. PMID: 26527777

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19. Sellappan S, Blackler A, Liao WL, O'Day E, Xu P, Thyparambil S, Cecchi F, Hembrough T, **Catenacci DVT**. Therapeutically induced changes in HER2, HER3, and EGFR protein expression for treatment guidance. *JNCCN* May 2016. 27160229

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22. Guo W, Ji Y, **Catenacci DVT**. A Subgroup Cluster Based Bayesian Adaptive Design for Precision Medicine. *Biometrics* 2016 Oct 24. doi: 10.1111/biom.12613.PMID:27775814

23. Javle MM, Bekaii-Saab T, Jain A, Wang Y, Kelley RK, Wang K, Kang HC, **Catenacci DVT**, Ali S, Krishnan S, Ahn D, Bocobo AG, Zuo M, Kaseb A, Miller V, Stephens PJ, Meric-Bernstam F, Shroff R, Ross J. Biliary cancer: Utility of next-generation sequencing for clinical management. *Cancer*. 2016 Sep 13. doi: 10.1002/cncr.30254. PMID: 27622582

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25. **Catenacci DVT,** Ang A, Shen J, Liao WL, Oliner KS, Loberg R, Rendak R, Xu P, Cecchi F, Burrows J, Hembrough T, Ruzzo A, Graziano F. MET Tyrosine Kinase Receptor Expression and Amplification as Prognostic Biomarkers of Survival in Gastroesophageal Adenocarcinoma. Epub *Cancer* 2016. PMID: 27926778

26. Bendell JC, Hochster H, Hart LL, Firdaus I, Mace JR, McFarlane JJ, Kozloff M, **Catenacci DVT**, Hsu JJ, Hack SP, Shames D, Phan SC, Cohn AL. Efficacy and safety results from a phase II randomised trial (GO27827) of first-line FOLFOX plus bevacizumab with or without onartuzumab in patients with metastatic colorectal cancer (mCRC). epub *The Oncologist.* PMID: 28209746

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Book Chapters:

93. **Catenacci DVT**, Cohen E., Villaflor V. Gastroesophageal Tumors: Principles and Practice. Chapter 33: Principles of Multimodality Therapy, pages 229-242. Mar 2009. (Edited by Jobe, Hunter and Thomas).

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1. **Catenacci DVT,** Chao J, Klempner S, Janjigian Y, Kim R, Liepa A, Kuder C, Chin S, Shah M, Fuchs C. A Systematic Review of First and Second Line Randomized Controlled Trials for Advanced Gastroesophageal Adenocarcinoma: Towards a Treatment Sequencing Strategy. *Manuscript in Preparation*
2. Grewal NKS, Serritella A, Peterson B, Moya S, Del Gaudio D, Das S, Lui P, Klempner S, **Catenacci DVT**. Assessment of FcgRIIIA single nucleotide polymorphisms on the efficacy of IgG1 monoclonal antibodies in patients with advanced gastroesophageal adenocarcinoma. *Manuscript in Preparation*
3. **Catenacci DVT,** Karrison T, Dignam J, Ji J. Statistical considerations of the 'Expansion Platform Clincial Trial Design Type II'. *Manuscript in preparation.*
4. Reizine N, Peterson B, Moya S, Wang S, Kanteti R, Tan YHC, **Catenacci DVT**. Targeted therapies for targeted populations: Met inhibition for *MET* amplified gastroesphageal adenocarcinoma. AMG DN Merck Serono TL *Manuscript in Preparation*
5. Reizine N, Veneris JT***, Peterson B, Moya S, Wang S, Tan YHC, Eng OS, Turaga K, Catenacci DVT. Targeted therapies for targeted populations: FGFR inhibition for FGFR2 amplification and/or fusion as for gastroesophageal adenocarcinoma. *Manuscript in Preparation*

RESEARCH SUPPORT:
Current Grant Support:

SU2C: Early Detection and Interception of Diffuse and Intestinal Gastric Cancer. (Andrew Chan, MGH. Co-Principal Investigator, (2020-2023) ($3 million, **Catenacci 20% effort).**
R01: Integration of genomic and phenotypic data for cancer research and clinical support. PI Yitan Zhu, Northshore. (2018-2023, Catenacci **effort 10%)**
General Research Fund: 2010-
Live Like Katie Foundation Award: 2013- ($300,000, **10% effort**)
Sal Ferrara Fund for PANGEA Award: 2014- ($300,000, **10% effort**)
Castle Foundation Award: 12/31/16-12/31/2020 ($250,000 over 4 years, **15% effort**)

Submitted/Planned Submission, Pending Grant Support:

Submitted: P30: 2021 Cancer Clinical Investigator Team Leadership Award (CCITLA) **15% effort**
Planned R01: Tumor Molecular and Immunologic Biomarker Heterogeneity in Gastroesophageal Adenocarcinoma. PI Catenacci **20% effort**
Planned: R01: Targeting Wild-Type Amplified KRAS and GNAS in Gastroesophageal Adenocarcinoma. PI Catenacci **20% effort**

Past Grant Support:
Amgen Hematology & Oncology Fellowship Grant. "The Role of RON Receptor Tyrosine Kinase in Gastroesophageal Cancers" (7/2008-06/2009).
CTSA-ITM Core Subsidies Fellow Grant. "Immunohistochemical Evaluation of The Role of RON and MET Receptor Tyrosine Kinases in Gastroesophageal Cancers" (1/09-06/09).
R21. "Novel Targeted Therapy in Pancreatic Cancer". Co-PI Salgia/Kindler (07/2009-06/2011).
ASCO 2009 Young Investigator Award. "The Role of RON (MST1R) Receptor Tyrosine Kinase in Gastroesophageal Cancers as a Therapeutic Target." (07/09-06/10).
Cancer Research Foundation Young Investigator Award (CRF YIA). "**The Role of RON Tyrosine Kinase in Gastroesophageal Cancer**". $75,000 5% effort (1/2011-12-2011).
American Research and Recovery Act (ARRA) NCI 8418. "GDC-0449 for Pancreas" A Randomized phase 2 trial of gemcitabine plus GDC-0449, a Hh pathway inhibitor, in metastatic pancreatic cancer. PI Salgia/Kindler. (07/09-06/13). **Laboratory Correlates** PI Catenacci. $35,000. 0% effort.
ALLIANCE/CALGB for Clinical Trials in Oncology Foundation YIA 07/2012-06/2013. "**Laboratory Correlatives Companion Study for CALGB 80101 Evaluating MET, RON, HER2, TOP2A and ERCC1 as Biomarkers for Gastroesophageal Adenocarcinoma."** $30,000, 0% effort (07/1/12 – 6/2014)
K-12. Paul Calabresi Clinical Oncology Career Development K12 Program.**"The Role of RON Tyrosine Kinase in Gastroesophageal Cancer".** $125,500/yr (10/1/10 – 9/30/13, 75% effort)

"**The role of RON tyrosine kinase in relation to targeted MET inhibition in gastroesophageal cancer**." OSI Pharmaceuticals. 04/23/2012 – 04/22/2014 ($140,000, 5% effort)
OncoPlex Diagnostics Collaborative Funding: OncoPlex Dx Project ID: Work Orders 3,4,6 ($24,500 each, 2012-2014, 0% effort)
UCCCC Pilot Precision Medicine Award. "**Towards Personalized Treatment of Gastroesophageal Adenocarcinoma: A Pilot Trial of PANGEA**" 01/01/14-12/31/14 ($35,000, 0% effort)
Amgen Collaborative Funding: Evaluation of MET expression and gene copy number in gastroesophageal tissues. 09/09/2013 – 09/08/2015 ($183,500, 0.5% effort)
ITM Pilot Award: Exhaustive detection of drug resistance mutations. 9/2015-9/2016 ($35,000, 0% effort). PI Chung-I Wu/Catenacci DVT.
K23. PANGEA–IMBBP Pilot Trial (**Personalized Antibodies for GastroEsophageal Adenocarcinoma Pilot Trial**). 9/11/14-8/31/17 ($156,000/yr, 75% effort).
PI Daniel Catenacci.
Genentech Collaborative Funding: Towards Personalized Therapy of Gastroesophageal Adenocarcinoma**.** ($250,000 10/2014-10/2017, 10% **effort**)
OncoPlex Diagnostics Collaborative Funding: OncoPlex Dx Project ID: Work Order 7. ($140,000/yr) ($280,000 1/14/15-1/13/18, 0% **effort**)
Endoscopic Research Award 2018 (PI Chapman) "Liquid Biopsies of the Portal Vein Using Endoscopic Ultrasound for Next Generation Sequencing of circulating tumor DNA for Therapeutic and Prognostic Stratification in Pancreatic Cancer." (2018-2019) ($60,000, 0% effort).
Ullman Scholar Award: "Evaluation of intratumoral tumor and immune cell heterogeneity" (7/2018-6-/2019 $50,000, 0% effort).
R01 5R01CA132897-07: Bayesian Inference for Tumor Heterogeneity with Next Generation Sequencing Data from PANGEA. PI Yuan Ji (Biostatistician Northshore/University of Chicago. (2015-2020) (Catenacci 10% effort)

ORAL PRESENTATIONS

Invited Speaking

International Meetings/Conferences

May 25, 2008. "RON receptor tyrosine kinase: A novel therapeutic target of gastroesophageal adenocarcinoma." Chinese National Genome Center, Shanghai, China.

May 26, 2008. "RON receptor tyrosine kinase: A novel therapeutic target of gastroesophageal adenocarcinoma." First Peoples' Hospital, Shanghai, China.

July 12, 2013 "Towards personalized treatment for gastroesophageal adenocarcinoma: strategies to address inter- and intra- patient tumor heterogeneity: PANGEA". WIN (Worldwide Innovative Networking in Personalized Cancer Medicine) 2013 5th Annual Conference. Paris, France. **Plenary Session ORAL Presentation & Best Abstract Award.**
http://ecancer.org/conference/328-win-symposium-2013/video/2151/strategies-to-address-inter--and-intra--patient-tumour-heterogeneity--pangea.php
http://www.winsymposium.org/abstracts/abstract-publication-2/
http://www.winsymposium.org/program/program-at-a-glance/presentations-july-12/

January 15, 2015 "Tumor Board: Management of Challenging Cases of Upper Gastrointestinal Cancers (ARS)" Invited Panelist. ASCO GI 2015, San Francisco, CA.

June 1, 2015 "Meeting Highlights: Gastrointestinal Cancer." ASCO Trainee & Early-Career Oncologist Lounge. ASCO 2015, Chicago IL.

January 21, 2016 GI ASCO Oral Abstract Session – Discussant. ASCO GI 2016, San Francisco, CA.

January 21, 2016 "General Session 3: Multimodal Approaches for Advanced GE Junction Cancers (East and West)--Challenging Cases" Session Chair. ASCO GI 2016, San Francisco, CA.

June 29, 2017 GI ESMO Oral Abstract Session - Session VI Gastric Cancer LBA-009: **Catenacci DVT**, Wainberg Z, Fuchs CS, Garrido M, Bang YJ, Muro K, Savage M, Wang J, Koshiji M, Dalal RP, Kang YK. KEYNOTE-059 cohort 3: safety and efficacy of pembrolizumab (pembro) monotherapy for first-line treatment of patients (pts) with PD-L1-positive advanced gastric/gastroesophageal (G/GEJ) cancer. ESMO World GI July 28-30, 2017. *Barcelona Spain***.** Oral Presentation, presented by Catenacci**.** Ann Oncol (2017) 28 (suppl_3): mdx302.008.

October 18, 2017 World CDx Annual Summit – Session: Clinical Implementation and Validation- "Improving Patient Recruitment and Retention on Precision Medicine Clinical Trials". World CDx 9th Annual Summit Boston, MA.

December 14, 2017 "Perioperative systemic chemotherapy and the practical use of triplet for borderline resectable mCRC patients". Chang Gung Memorial Hospital, Linkou District, Taiwan.

December 16, 2017 "Annual update on the treatment for metastatic colorectal cancer and its impact on personalized therapeutic approach." Annual Meeting of the Society of Colon and Rectal Surgeons. Taipei, Taiwan**.**

June 19, 2018 "Gastroesophageal tumor molecular heterogeneity, molecular evolution, and implications in the clinic" Samsung Medical Center. Seoul, Korea.

June 21, 2018 Korean Cancer Association GI Gastric Cancer Plenary Session: "Overcoming tumor heterogeneity in Gastroesophageal Adenocarcinoma: the PANGEA trial" Korean Cancer Association Annual Meeting. Seoul, Korea.

September 27, 2018 2nd Annual AACR Conference Translational Medicine, Session: Precision Cancer Medicine: "Implementing precision strategies to address molecular heterogeneity for gastroesophageal adenocarcinoma". Sao Paolo, Brazil.

May 9, 2019 13th International Gastric Cancer Congress, Session Novel Drugs (Non-immune therapy): "Personalized treatment: How to overcome tumor heterogeneity". Prague, Czech Republic.

June 3, 2019 ASCO 2019 Annual Meeting, Educational Session: Debate: This House Believes FLOT Is the Standard Treatment for Fit Patients With T3N1 GEJ Adenocarcinoma. Chicago IL, USA.

September 9, 2019 "Overcoming tumor heterogeneity in Gastroesophageal Adenocarcinoma: the PANGEA trial." Eleventh International Workshop on Pharmacodynamics of Anticancer Agents. Monestier, France.

October 19, 2019 "The role of anti-HER2 therapy in the management of Gastro-Esophageal Adenocarcinoma: Metastatic, Adjuvant, and Neo-adjuvant Settings?" Annual McGill Symposium on Upper GI malignancies. Montreal, Canada.

January 23, 2020 GI ASCO Oral Abstract Session – Discussant. ASCO GI 2020, San Francisco, CA.

March 3, 2020 Japanese Annual Gastric Cancer Meeting - Targeted therapies for targeted populations in Gastric cancer (PANGEA), Yokohama, Japan.

National

January 13, 2010 Visiting Professor Lecture: "RON is a novel prognostic marker and therapeutic target for gastroesophageal adenocarcinoma." Northwestern University, Chicago, IL.

March 12-14, 2010 "Novel therapies for gastroesophageal adenocarcinoma: A personalized treatment approach." World Congress on Gastroenterology & Urology. Marriott Omaha, USA.

June 21, 2011. "RON tyrosine kinase in cancer: no longer MET's Little Brother!" OSI/Astellas Pharmaceuticals. Farmingdale, Long Island, NY.

June 24, 2011. "RON tyrosine kinase in cancer: no longer MET's Little Brother!" AVEO Pharmaceuticals, Inc. Cambridge, MA.

October 5, 2011. "Targeted Therapies A New Generation of Cancer Treatments." OptumHealth's 20th Annual National Conference. Hyatt Regency in Minneapolis, MN.

October 20, 2011 "A Patient with Gastric Cancer Treated with a MET Inhibitor." Expert Forum on MET Inhibition. Oncology Network for Excellence. NCIR/CTEP, Bethesda, MD..

October 21, 2011. "Predicting Response to MET Targeted Agents with Biomarkers: *MET* Amplification." Expert Forum on MET Inhibition. Oncology Network for Excellence. NCI/CTEP, Bethesda, MD.

February 22-25, 2012. "MET tyrosine kinase: prognostic and predictive biomarkers of the MET pathway." 12th Annual Targeted Therapies of Lung Cancer Meeting. The Fairmont Miramar Hotel, Santa Monica, CA. Sponsored by the IASLC.

September 20, 2012. "Towards personalized treatment for gastroesophageal adenocarcinoma: strategies to address inter- and intra- patient tumor heterogeneity," Genentech, San Francisco.

October 25-26, 2012. "Gastrointestinal Cancer Overview: Gastroesophageal Adenocarcinoma, Colorectal Adenocarcinoma, Hepatocellular Carcinoma. FOCUS on MET Tyrosine Kinase." 2nd Annual Expert Forum on MET Inhibition. Oncology Network for Excellence. CTEP/NCI. Washington, DC.

October 25-26, 2012. "Gastroesophageal Adenocarcinoma: Strategies to address inter- & intra-patient tumor heterogeneity…a focus on MET." 2nd Annual Expert Forum on MET Inhibition. Oncology Network for Excellence. CTEP/NCI. Washington, DC.

October 25-26, 2012. "Colorectal Cancer: FOCUS on MET Tyrosine Kinase." 2nd Annual Expert Forum on MET Inhibition. Oncology Network for Excellence. CTEP/NCI. Washington, DC.

December 6, 2012. "Towards personalized treatment for gastroesophageal adenocarcinoma: strategies to address inter- and intra- patient tumor heterogeneity…PANGEA." AVEO Pharmaceuticals, Inc. Cambridge, MA.

April 5, 2013. "Moderated Roundtable Discussion: Defining the major knowledge gaps and priorities for future research of cholangiocarcinoma". Invited Panelist. CanLiv 3rd Annual Symposium: Harnessing Genomic-Driven Therapies for Hepatobiliary Cancers. Washington, DC.

May 18, 2013. "Treatment of Advanced Gastroesophageal Cancer: A Focus on Targeted Therapies" JACOB phase III Clinical Trial Investigators' Meeting: A double-blind, placebo-controlled, randomized, multicenter Phase III Study evaluating the efficacy and safety of pertuzumab in combination with trastuzumab and chemotherapy in patients with HER2-positive metastatic gastroesophageal junction and gastric cancer. International Investigator Meeting. InterContinental, Chicago, IL.

June 20-22, 2013. "Gastroesophageal Adenocarcinoma in The Era of Targeted Therapies: A Focus on MET" Amgen Oncology Global Advisory Board. Thousand Oaks, CA.

May 4-6, 2014. Detection of Portal Vein (PV) Circulating Tumor Cells (CTCs) in Pancreatic Cancer (PC) patients obtained by EUS guided PV Sampling. A safety and Feasibility trial. Accepted as an **Oral Presentation**. Digestive Disease Week 2014. Chicago, IL.

November 24, 2014 Visiting Professor Lecture: "Strategies to address inter- and intra- patient tumor molecular heterogeneity using next-generation companion diagnostics and PANGEA: a novel clinical trial design". Nantworks/NantHealth, Los Angeles, CA.

March 3, 2015. Visiting Professor Lecture: "Strategies to address inter- and intra- patient tumor molecular heterogeneity using next-generation companion diagnostics and PANGEA: a novel clinical trial design". Grand Rounds University of California San Diego UCSD, CA.

March 5, 2015. Visiting Professor Lecture: "Strategies to address inter- and intra- patient tumor molecular heterogeneity using next-generation companion diagnostics and PANGEA: a novel clinical trial design". Section of Oncology Weekly Meeting, Stanford University. Palo Alto, CA.

March 30/31, 2015. "Next-Generation Clinical Trials Incorporating Next-Generation Companion Diagnostics". OMICS 2nd Annual Meeting, Patrick Soon-Shiong NantOmics. Los Angeles, CA.

July 16, 2015. "Next-Generation Clinical Trials Incorporating Next-Generation Companion Diagnostics". FDA gastric cancer mini-symposium. Silver Spring, MD.

November 7, 2015 Debbie's Dream Foundation for Stomach Cancer Inaugural Chicago Symposium. Committee Chair and Organizer, Moderator, Speaker ("Tumor Genomics, Immunotherapy, Clinical Trials, and Other Hopes for the Future"), O'Hare Marriot, Chicago IL.

November 14, 2015. "Tumors to the Liver: Metastatic Adenocarcinoma of Unknown Origin – Work up before Therapy and Role of Molecular Profiling to Sort it out" Hepatic Tumor Summit, Tampa FL.

November 14, 2015. "Does Molecular Profiling Predict Response to Therapy?" Hepatic Tumor Summit, Tampa FL.

June 17, 2016. Visiting Professor Lecture: "Tumor molecular heterogeneity, molecular evolution, and implications in the clinic." Roswell Park Grand Rounds, Buffalo NY.

October 1, 2016. "Tumor Genome Analysis Includes Germline Genome!! Are We Ready For Surprises??" National Society of Genetic Counsellors 35th Annual Meeting. Seattle WA.

October 26, 2016. Visiting Professor Lecture: "Determining the Clinical Utility of Plasma ctDNA Next-Generation Sequencing". Guardant Health. Redwood City, CA.

May 12, 2017. "Addressing Tumor Molecular Heterogeneity using A Novel Clinical Trial Design – PANGEA". Symposium on Dose Selection for Cancer Treatment Drugs: Novel Clinical Trial Designs for Cancer Treatments. Stanford, Palo Alto, California.

Novermber 3, 2017. "KEYNOTE-059: Trial Efficacy and Safety of Pembrolizumab Alone or in Combination With Chemotherapy in Advanced Gastric or Gastroesophageal Cancer." KEYNOTE-585 National Initiation Investigator Meeting, Hilton Dallas Lincoln Centre, Dallas, Tx.

January 16, 2018. Visiting Professor Lecture: "Intra-patient molecular heterogeneity a barrier to successful implementation of precision medicine in gastroesophageal adenocarcinoma – how to address?." GI Oncology Grand Rounds University of California, San Francisco University of California San Francisco UCSF. San Francisco, CA.

February 13, 2018. Visiting Professor Lecture: "Tumor molecular heterogeneity, molecular evolution, and implications in the clinic." Cancer Center Seminar, University of Texas Southwestern, Dallas, TX.

April 21, 2018. "Chemotherapy, Targeted Treatments, and Immunotherapy for Gastric and Esophageal Cancer: Hope for the Future". Debbie's Dream Foundation for Stomach Cancer 8th Annual Symposium and Live Webcast. Hollywood, FL.

August 4, 2018. "Best of ASCO 2018 : Gastrointestinal (Non Colorectal) Cancer". Best of ASCO 2018, Denver, CO.

August 6, 2018. Visiting Professor Lecture: "Tumor molecular heterogeneity, molecular evolution, and

implications in the clinic." Cancer Center Seminar. Yale University Medical Center. New Haven, CT.

November 2, 2018. "Gastroesophageal Adenocarcinoma Overview of Epidemiology, Molecular Profiling and Treatment." Phase III FIGHT study Investigator Meeting: A Study of Bemarituzumab (FPA144) Combined With Modified FOLFOX6 (mFOLFOX6) in Gastric/Gastroesophageal Junction Cancer (FIGHT). The Westin Austin Downtown. Austin, Tx.

January 12, 2019. ""Tumor molecular heterogeneity, molecular evolution, and implications in the clinic – testing a treatment algorithm." Cancer Center Showcase – Precision Oncology Applications and Utility at Cancer Centers Session. The Precision Medicine World Conference (PMWC) 2019. Santa Clara, CA.

April 17, 2019. "Next-Generation Precision Oncology Trials". The 3rd Annual Stat4Onc Conference. Hartford, CT.

June 29, 2018. "Best of ASCO 2019: Gastrointestinal (Colorectal) Cancer". Best of ASCO 2019, St. Louis MO.

July 17, 2019. Visiting Professor Lecture: "Assessing and Addressing Tumor Genomic Heterogeneity: Plasma ctDNA Next-Generation Sequencing." Roswell Park Cancer Center, Buffalo, NY.

August 26, 2019. "Assessing and Addressing Tumor Genomic Heterogeneity: Plasma ctDNA Next-Generation Sequencing." Moffitt, Tampa, FL.

October 10, 2019. "Novel Targets and Immunotherapy Advances in Esophagogastric Adenocarcinoma How do we Sequence New Immunotherapy Agents?" International Society of Gastrointestinal Oncology (ISGIO) Annual Meeting. Arlington, VA.

November 4, 2019. "Gastric Cancer: Molecular subtypes and targeted therapy potential." Collaborative Group of the Americas on Inherited Gastrointestinal Cancer (CGA-IGC) Annual Meeting. Salt Lake City, UT.

March 7, 2020. "Perioperative Chemotherapy With or Without Radiation in Patients with Early Stage Gastro-Esophageal Cancers." Panel. Mayo Clinic Gastrointestinal Cancers 2020. San Diego, CA.

March 7, 2020. " Metastatic Refractory GE Cancer: Where Should Immunotherapy Fit into the Treatment Algorithm?" Mayo Clinic Gastrointestinal Cancers 2020. San Diego, CA.

February 18, 2021 "Advances in the management of Gastroesophageal Adenocarcinoma." UChicago Medicine virtual CME on the Management of Metastatic Gastric Cancer

February 26, 2021. "Utilization of Molecular Analysis in Oncology Practice." Henry Ford Health System Grand Rounds. Detroit, MI.

Regional

March 13, 2009 "Targeting Hedgehog Signaling in Cancer," The University of Chicago Phase II Consortium 14th Annual Symposium, Gleacher Center, Chicago, IL.

March 13, 2010. "Targeting Hedgehog Signaling in Cancer," The University of Chicago Phase II Consortium 15th Annual Symposium, Gleacher Center, Chicago, IL.

May 6, 2011. "Perioperative Therapy for Gastroesophageal Adenocarcinoma". The 3rd Annual Controversies in the Management of Complex GI Patients Symposium. The Ritz Carlton Hotel, Chicago, IL.

September 16, 2011. "A Laboratory Correlative Companion Study for CALGG 80101 evaluating MET, RON, HER2, TOP2A, and ERCC1 as Biomarkers for Gastroesophageal Adenocarcinoma" ACTION (Alliance for Clinical Trials In Oncology Group). Hyatt Regency O'Hare, Rosemont, IL.

Sept 15-18, 2011. "Developmental Therapeutics in Oncology: Updates from ASCO 2011 Best of ASCO Meeting". The 14th Annual APAO Conference. APAO's Best of ASCO Oncology Meeting. The Chicago Wyndham Hotel.

April 27, 2012. "Pancreatic Cancer: Hedgehog Signaling & the new era of FOLFIRINOX". The University of Chicago Phase II Consortium 17th Annual Symposium, Gleacher Center, Chicago.

April 27, 2012. "Towards Personalized Cancer Care for Gastroesophageal Adenocarcinoma: Challenge, Controversy & Consensus," The University of Chicago Phase II Consortium 17th Annual Symposium, Gleacher Center, Chicago.

September 07, 2012. "Systemic Therapy for Hepatocellular Carcinoma (HCC) and Biliary Tract Cancers," The 4th Annual Gastrointestinal Cancer Symposium: Update on the Management of GI Cancer Patients. The Ritz Carlton Hotel, Chicago, IL.

April 12, 2013. "Towards personalized treatment for gastroesophageal adenocarcinoma: strategies to address inter- and intra- patient tumor heterogeneity…PANGEA," The University of Chicago Phase II Consortium 18th Annual Symposium, Gleacher Center, Chicago.

October 10, 2014 "Personalized Colon Cancer Care: Are we there yet?" University of Chicago Symposium: "Colon, Rectum and Beyond: Innovations in Management of Inflammatory Bowel Disease, Colorectal Cancer and Pelvic Floor Disorders".The Board of Regents Room, American College of Surgeons, North St. Clair, Chicago, IL.

January 23, 2015 "Strategies to address inter- and intra- patient tumor molecular heterogeneity using next-generation companion diagnostics and PANGEA: a novel clinical trial design". Grand Rounds Northshore Hosptial, Chicago, IL.

April 13, 2015 "Strategies to address inter- and intra- patient tumor molecular heterogeneity using next-generation companion diagnostics and PANGEA: a novel clinical trial design". NorthShore Scientific Society meeting, Chicago, IL.

November 5, 2015 "Analyzing Your Genome". Rolfe Foundation Symposium on Personalized Medicine. Cancer Wellness Center, Northbrook, IL.

April 8, 2016. "Tumor Molecular Hetergeneity, Molecular Evolution, and Implications in the clinic" The University of Chicago Phase II Consortium 21th Annual Symposium, Gleacher Center, Chicago.

November 7, 2017. "Personalized Medicine in the Gastrointestinal Oncology Clinic: Promises, Challenges, and Future Decisions". NorthShore Gut Club Quarterly Meeting. Skokie, IL.

April 20, 2018. Translational Research in Upper GI Cancers: Gastroesophageal Cancer & Cholangiocarcinoma." The University of Chicago Phase II Consortium 23rd Annual Symposium, Gleacher Center, Chicago.

Intramural

November, 2006 "Anticoagulants, Hemostasis, and Cancer – is the link c-MET? Case Presentation and Review of the literature." University of Chicago Hematology/Oncology Section Conference.

June 25, 2007 "Cancer Stem Cells". University of Chicago Hematology/Oncology Section Conference..

Oct 27, 2008 "RON Tyrosine Kinase: A Novel Molecular Target for the Treatment of Gastroesophageal Cancer." University of Chicago Hematology/Oncology Section Conference.

Sept 14, 2009 "The Role of RON Receptor Tyrosine Kinase in Gastroesophageal Cancers – Why MET is Not Enough" University of Chicago Hematology/Oncology Section Conference.

Chicago, IL, April 19, 2011. "Adjuvant Chemotherapy for Colon Cancer: Towards a Personalized Approach". University of Chicago Department of Surgery Colorectal Cancer Conference.

August 3, 2011. "Career Development Seminar for Summer Research Students". University of Chicago Laboratories.

August 29, 2011 "RON tyrosine kinase in cancer: no longer MET's Little Brother!" University of Chicago Hematology/Oncology Section Conference.

October 10, 2011. "Novel Molecularly Targeted Therapies in Esophageal Cancer: Relevance of MET&RON" Lederer Foundation Annual Meeting. University of Chicago, Chicago, IL.

October 26, 2011. "Current trends in Colon Cancer Therapy: agents and approach" CANCER BIOLOGY 1: HUMAN CANCER PRESENTATION AND MODELING,

October 31, 2012 "Current trends in Colon Cancer Therapy: agents and approach" CANCER BIOLOGY 1: HUMAN CANCER PRESENTATION AND MODELING,.

November 27, 2012. "Adjuvant Chemotherapy for Colon Cancer: Towards a Personalized Approach". University of Chicago Department of Surgery Colorectal Cancer Conference. Chicago, IL,

November 14, 2012 "RON upregulation is a resistance mechanism to MET directed therapy in MET driven models." University of Chicago Department of Medicine Section of Hematology/Oncology Research Seminar, Chicago, IL.

September 25, 2013. "MET Tyrosine Kinase and GI Cancers." University of Chicago Department of Medicine Section of Hematology/Oncology AbbVie Meeting KCBD, Chicago, IL,

February 14, 2014. "Strategies to address inter- and intra- patient tumor molecular heterogeneity using next-generation companion diagnostics and PANGEA: a novel clinical trial design". UCCCC Translational Seminars.

February 12, 2016. "Tumor molecular heterogeneity, molecular evolution, and implications in the clinic". UCCCC Translational Seminars.

June 14, 2016: "Treatment of Locally Advanced and Advanced Esophagogastric Cancer". Thoracic Surgery Fellows Conference, Chicago, IL.

March 6, 2017. Genomic Heterogeneity as a Barrier to Precision Medicine for Gastroesophageal Adenocarcinoma: An update on PANGEA. Hematology/Oncology Section Monday Conference.

April 19, 2019. "Assessing and Addressing Tumor Genomic Heterogeneity: Plasma ctDNA Next-Generation Sequencing." UCCCC Translational Seminars.

June 24, 2019. "Targeted Therapies for Gastroesophageal Adenocarcnioma." Third annual UChicago-AbbVie Oncology Symposium. University of Chicago, Chicago, IL.

July 22, 2019. "Perioperative therapy for Gastroesophageal Adenocarcinoma." Surgical Oncology Fellow Conference. University of Chicago, Chicago, IL.

INVITED, ELECTED SERVICE:

2010-2015	University of Chicago Clinical Trials Research Committee (CTRC) member
2011-	Agency for Healthcare Research and Quality (AHRQ) case reviewer, US Department of Health and Human Services.
2012-13, 2014-17	Esophago-Gastric NCI Task Force, ALLIANCE Junior Member
2013-2015	RILOMET-1 Amgen Phase III Trial Steering Committee Member
2014-2016	University of Chicago BSD Institutional Review Board (IRB) member

2014-	Data Safety Monitoring Committee**:** EMD Serono anti-PDL1 phase I trial.
2014-	Cholangiocarcioma Foundation Medical Advisory Committee Member
2015-	Debbie's Dream Foundation for Stomach Cancer Medical Advisory Committee Member
2015-	Physician Lead for the University of Chicago Cancer Center Genomic Project
2015	DOD Peer Review: Ad Hoc Reviewer Stomach Cancer
2015-2017	Hematology/Oncology Monthly Molecular Pathology Tumor Board Co-Chair
2016-	Biospecimens Committee Member
2017-	ASCO Esophageal Cancer Guideline Expert Panel Member
2018-	AACR Gastrointestinal Cancer Research Grants Scientific Review Committee – Gastric
2018-	DoD FY18 Peer Reviewed Cancer Research Program (PRCRP) – Gastric
2018-2020	ASCO SEP 7th edition Co-author (with B. Polite) for GI Chapter
2020-	SWOG Vice Chair the GI Translational Medicine Subcommittee
2020-	Society of Thoracic Surgeons STS & ASTRO Clinical Practice Guidelines on Multimodality Treatment of Esophageal Cancer Expert Panel Member

Editorial Activities

***Ad hoc* Reviewer:**

Journal of Clinical Oncology JCO	*Pharmacogenomics Journal*	*Tumor Biology*
JCO Precision Oncology JCO PO	*Mayo Clinic Proceedings*	*JNCCN*
New England Jounral of Medicine	*Clinical Practice*	*Lancet Oncology*
Nature Reviews Disease Primers	*Current Cancer Drug Target*	*Future Medicine*
Expert Review of Anticancer Therapy	*Clinical Investigation*	*Future Oncology*
Journal of National Cancer Institute	*Molecular Cancer Research*	*Cancer*
Inflammation & Allergy Drug Discovery	*Trends in Molecular Medicine*	*Cancer Discovery*
Histology and Histopathology	*The Oncologist*	*Colorectal Cancer*
World Journal of Gastroenterology (WJO)	*Targeted Oncology*	*Oncotarget*
Clinical Cancer Research	*Molecular Cancer Therapeutics*	*JAMA Oncol*
Cancer Cell	*Br J Cancer*	*Cancers*

Associate Editor:
1/2019-present *Journal of American Medical Association Network Open* (*JAMA Network Open*); Oncology

Editorial Board Membership:
1/2015 – 4/2018 *World Journal of Clinical Oncology (WJCO)*
7/2016 – present *Journal of Clinical Oncology (JCO) Precision Oncology*
1/2017 – present *Cancer*
8/2020 – present *Cancers*

CLINICAL PROTOCOLS:

International PI

A Phase 2/3 Trial to Evaluate Margetuximab in Combination with INCMGA00012 and Chemotherapy or MGD013 and Chemotherapy in Patients with Metastatic or Locally Advanced, Treatment-naïve, HER2-Positive Gastric or Gastroesophageal Junction Cancer Open to Accrual 12/5/19

An International Phase 1/2 Study of GRT-C901/GRT-R902, a Personalized Neoantigen Immunotherapy, in Combination with Immune Checkpoint Blockade for Patients with Advanced Solid Tumors Open to Accrual 9/2018

FIGHT: A Phase 1/3 Study of FPA144 versus Placebo in Combination with Modified FOLFOX6 in Patients with Previously Untreated Advanced Gastric and Gastroesophageal Cancer. Open to Accrual 5/2018

A Phase 1b/2 Open Label, Dose Escalation Study of Margetuximab in Combination with Pembrolizumab in Patients with Relapsed/Refractory Advanced HER2+ Gastroesopahgeal Junction or Gastric Cancer. Open to accrual 4/2016

A Phase II Clinical Trial of Pembrolizumab as Monotherapy and in Combination with Cisplatin+5-Flourouracil in Subjects with Recurrent or Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma (KEYNOTE 059). Open to accrual August 2015; closed to accrual 4/2016

- **Oral presentation World GI ESMO, cohort 1**
- **Author cohorts 1, 2, and 3**

A Phase III, Multicenter, Randomized, Double-Blind, Placebo Controlled Study of Rilotumumab (AMG 102) with Epirubicin, Cisplatin, and Capecitabine (ECX) as First-line Therapy in Advanced MET-Positive Gastric or Gastroesophageal Junction Adenocarcinoma. (RILOMET-1) Amgen. Open to accrual January 2013, *Terminated November 2014. Closed to accrual.*

- **RILOMET-1 Steering Committee Member**
- **Senior Author on final analysis abstract ASCO 2015, first author manuscript .**

National PI

NCI-MATCH – *MET* amplified (C1 Arm) and exon 14 deletion (C2 Arm) arms (Crizotinib) **Translational Correlatives Chair**. Open to enrollment 5/2016.

A Phase 1 Open-Label, Dose-Finding Study Evaluating Safety and Pharmacokinetics of FPA144 in Patients with Advanced Solid Tumors. Open to accrual January, 2016. Closed.

Investigator Initiated Trials PI:

Use of Trifluridine/ Tipiracil (TAS-102) and Oxaliplatin as Induction Chemotherapy in Resectable Esophageal and Gastroesophageal Junction (GEJ) Adenocarcinoma. Pending opening

A phase I/II trial of Rucaparib in combination with Ramucirumab with or without Nivolumab in previously treated patients with advanced gastric and esophageal adenocarcinoma (RiME). Open to accrual 9/29/20

A Phase 1 dose finding study of the gFOLFOXIRITAX regimen using UGT1A1 genotype-directed Irinotecan with Fluorouracil, Leucovorin, Oxaliplatin and Taxotere in patients with untreated advanced upper gastrointestinal adenocarcinomas: The I-FLOAT Study. Open to Accrual 3/25/2020

A window of opportunity study of pembrolizumab in colon cancer. Open to Accrual 1/17/2020

A Phase IIa Study of Laparoscopic Hyperthermic Intraperitoneal Chemotherapy (HIPEC) and PD-L1 Expression in Gastric Cancer with Peritoneal Metastases Open to Accrual. 11/7/19

A Phase II Trial of Neoadjuvant Pembrolizumab for Resectable Early Stage Gastroesophageal Adenocarcinoma Open to Accrual. 10/11/19

PANGEA -1MBBP Trial (Personalized Antibodies for GastroEsophageal Adenocarcinoma Pilot Trial) – NCT02213289. Open to accrual.

A pilot trial of perioperative mFOLFIRINOX with UGT1A1 genotyping for gastroesophageal adenocarcinoma – open to accrual 11/2014 - NCT02366819.

Understanding the Role of Genetics in Solid Tumor Malignancies. IRB 15-0443. Open to accrual 2/2016. PI: J Churpek, D Catenacci, H. Kindler. University of Chicago Medical Center.

A Multicenter Randomized Placebo-controlled Phase 2 Trial of Gemcitabine plus GDC-0449 (NSC 747691), a Hedgehog Pathway Inhibitor, in Patients with Metastatic Pancreatic Cancer (10052747). NCI/CTEP #8418. Opened to accrual Sept 1, 2009. (ARRA funded) *Closed to accrual*

Co-PI: H Kindler, D Catenacci, University of Chicago Medical Center.

- Laboratory and Radiological Correlatives, D Catenacci
- Interim Analysis presented as Poster Discussion at ASCO 2012
- Final Analysis to be presented as Poster Discussion at ASCO 2013
- *Manuscript published JCO 9/2015*

2007-present: GI Tissue Banking Protocols:

- **Retrospective IRB 16146B – currently accruing**
- **Prospective Procurement IRB 16294A– currently accruing**
- **Prospective Procurement IRB XX – Internal NGS 1212 gene molecular panel**

PI: D Catenacci, University of Chicago Medical Center.

2004: Phase I/II Clinical Trial of Azacytidine and Arsenic Trioxide combination treatment of Myelodysplastic Syndromes.
PI: G Schiller, UCLA Medical Center. *Closed to accrual*

Site PI Pharma Sponsored:

A Phase 2, multicenter open-label, non-randomized study of bavituximab plus pembrolizumab in patients with advanced gastric or gastroesophageal cancer who have progressed on or after at least one prior standard therapy. Open to Accrual 1/21/20.

A Phase 2/3 Trial to Evaluate Margetuximab in Combination with INCMGA00012 and Chemotherapy or MGD013 and Chemotherapy in Patients with Metastatic or Locally Advanced, Treatment-naïve, HER2-Positive Gastric or Gastroesophageal Junction Cancer Open to Accrual 12/5/19

A Phase 2, open-label, single-arm trial of trastuzumab deruxtecan (DS-8201a) in HER2-positive, unresectable or metastatic gastric or gastro-esophageal junction (GEJ) adenocarcinoma subjects who have progressed on or after a trastuzumab-containing regimen. 10/1/19

A Phase 1 study of ZW49 in patients with locally advanced (unresectable) or metastatic HER2-expressing cancers. Open to Accrual 8/29/19

A Phase 3, Global, Multi-Center, Double-Blind, Randomized, Efficacy Study of IMAB362 Plus mFOLFOX6 Compared with Placebo Plus mFOLFOX6 as First-line Treatment of Subjects with Claudin (CLDN)18.2-Positive, HER2-Negative, Locally Advanced Unresectable or Metastatic Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma. *Open to Accrual 2/1/19.*
Trial Steering Committee Member.

An International Phase 1/2 Study of GRT-C901/GRT-R902, a Personalized Neoantigen Immunotherapy, in Combination with Immune Checkpoint Blockade for Patients with Advanced Solid Tumors *Open to* Accrual 9/2018

A Phase 1/2 Study of FPA144 versus Placebo in Combination with Modified FOLFOX6 in Patients with Previously Untreated Advanced Gastric and Gastroesophageal Cancer. Open to Accrual 5/2018 Closed to accrual

A Phase 1/2, Open-Label, Safety, Tolerability, and Efficacy Study of Epacadostat in Combination with Pembrolizumab and Chemotherapy in Subjects with Advanced or Metastatic Solid Tumors (ECHO-207/KEYNOTE-723). Open to accrual 11/2017 Closed to accrual

Combination with Cisplatin and 5-Fluorouracil versus Placebo in Combination with Cisplatin and 5-Fluorouracil as First-Line Treatment in Subjects with Advanced/Metastatic Esophageal Carcinoma (KEYNOTE-590). Open to accrual 10/2017 Closed to accrual

A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of AG-120 in Previously-Treated Subjects with Nonresectable or Metastatic Cholangiocarcinoma with an IDH1 Mutation Open to accrual May 2017 Closed to accrual

A Randomized, Multicenter, Double Blind, Phase III Study of Nivolumab or Placebo, in Subjects with Resected Lower Esophageal, or Gastroesophageal Junction Cancer. Open to accrual 8/2016. Closed to accrual Closed to accrual

A Phase 1b/2 Open Label, Dose Escalation Study of Margetuximab in Combination with Pembrolizumab in Patients with Relapsed/Refractory Advanced HER2+ Gastroesopahgeal Junction or Gastric Cancer. Open 4/2016. Closed to accrual

A Phase II, Open-Label, Single-Arm, Multicenter Study to Evaluate the Efficacy and Safety of INCB054828 in Subjects with Advanced/Metastatic or Surgically Unresectable Cholangiocarcinoma Including FGFR2 Translocations who Failed Previous Therapy Closed to accrual 10/2018

A Phase 1b/2 Study of MEDI4736 in Combination with Tremelimumab, MEDI4736 Monotherapy, and Tremelimumab Monotherapy in Subjects with Metastatic or Recurrent Gastric or Gastroesophageal Junction Adenocarcinoma. Closed to accrual 5/2018

A Phase 1b Open-Label Study of PEGylated Recombinant Human Hyaluronidase (PEGPH20) Combined with Pembrolizumab in Subjects with Selected Hyaluronan-High Solid Tumors. Closed to accrual 4/2018.

A Phase 2, Open-Label, Randomized Study to Evaluate the Efficacy and Safety of GS-5745 Combined with Nivolumab versus Nivolumab Alone in Subjects with Unresectable or Recurrent Gastric or Gastroesophageal Junction Adenocarcinoma. Closed to accrual 4/2017

Randomized, Double-Blind Phase 3 Study Evaluating TAS-102 Plus Best Supportive Care (BSC) Versus Placebo Plus BSC in Patients with Metastatic Gastric Cancer Refractory to Standard Treatments. Open to Accrual 4/2016, closed to accrual 11/30/17

A Phase 2, Open-label Evaluation of CRS-207 and Pembrolizumab in Adults with Recurrent or Metastatic Gastric, Gastroesophageal Junction, or Esophageal Adenocarcinomas. Terminated early.

A Randomized, Active-Controlled, Partially Blinded, Biomarker Select, Phase III Clinical Trial of Pembrolizumab as Monotherapy and in Combination with Cisplatin+5-Fluorouracil versus Placebo+Cisplatin+5-Fluorouracil as First-Line Treatment in Subjects with Advanced Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma (KEYNOTE 062). Open to Accrual 3/2016 Closed to Accrual 6/2017.

A021302: Impact of Early FDG-PET Directed Intervention on Preoperative Therapy for Locally Advanced Gastric Cancer: A Random Assignment Phase II Study. Open to accrual October 2015.

A Phase 1 Open-Label, Dose-Finding Study Evaluating Safety and Pharmacokinetics of FPA144 in Patients with Advanced Solid Tumors. Open to accrual January, 2016. Closed.

A Phase II Clinical Trial of Pembrolizumab as Monotherapy and in Combination with Cisplatin+5-Flourouracil in Subjects with Recurrent or Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma (KEYNOTE 059). Open to accrual August 2015; closed to accrual 4/2016

ARQ197-A-U303 A Phase III, Randomized, Double-Blind Study of Tivantinib (ARQ 197) in Subjects with MET Diagnostic-High Inoperable Hepatocellular Carcinoma (HCC) Treated with One Prior Systemic Therapy. Open to accrual January 2013. Closed to accrual.

A Double-Blind, Placebo-Controlled, Randomized, Multicenter Phase III Study Evaluating the Efficacy and Saftery of Pertuzumab in Combination with Trastuzumab and Chemotherapy in Patients with Her2-Positive Metastatic Gastroesophageal Junction and Gastric Cancer (JACOB study). Open to accrual July 2013. Closed to accrual.

A phase I open-label, non-randomized, dose-escalation first-in-man trial to investigate the c-Met kinase inhibitor EMD 1214063 under two different regimens in subjects with advanced solid tumors. Phase I expansion for MET amplification. Open to accrual November, 2013. Closed to accrual.

Phase Ib Multi-Cohort Study of MK-3475 in Subjects with Advanced Solid Tumors - Gastric/EGJ cohort PI for anti-PD1 inhibitor. Open to accrual November, 2013. Closed to accrual.

Phase 1, First-in-Human Study Evaluating the Safety, Tolerability, and

Pharmacokinetics of AMG 337 in Adult Subjects with Advanced Solid Tumors. Open to accrual September 2013. Closed to accrual.

A Phase III, Multicenter, Randomized, Double-Blind, Placebo Controlled Study of Rilotumumab (AMG 102) with Epirubicin, Cisplatin, and Capecitabine (ECX) as First-line Therapy in Advanced MET-Positive Gastric or Gastroesophageal Junction Adenocarcinoma. (RILOMET-1) Amgen. Open to accrual January 2013, Terminated November 2014. Closed to accrual.

- *RILOMET-1 Steering Committee Member*
- ***Senior Author on efficacy abstract ASCO 2015***

A *Randomized, Phase III, Multicenter, Double-Blind, Placebo-Controlled Study Evaluating The Efficacy And Safety Of Onartuzumab (Metmab) In Combination With 5-Fluorouracil, Folinic Acid, And Oxaliplatin (MFOLFOX6) In Patients With Metastatic HER2-Negative, Met-Positive Gastroesophageal Cancer. Open to accrual July 2013. Closed to accrual.*

A Pilot Study of neoadjuvant and adjuvant mFOLFIRINOX in localized, resectable pancreatic adenocarcinoma. Co-PI (Kindler). Closed to accrual.

A Phase 2b Randomized, Open-Label Trial of JX-594 (Vaccinia GM-CSF / TK-deactivated Virus) Plus Best Supportive Care Versus Best Supportive Care in Patients with Advanced Hepatocellular Carcinoma Who Have Failed Sorafenib Treatment. Jennerex. Closed to accrual.

ECOG E1208: A Phase III Randomized Trial of Chemoembolization with or without Sorafenib in Unresectable Hepatocellular Carcinoma (HCC) in Patients with and without Vascular Invasion. Closed to accrual.

CALGB 80802: Phase III randomized study of sorafenib (IND 69896, NSC 724772) plus doxorubicin versus sorafenib in patients with advanced hepatocellular carcinoma (HCC). Closed to accrual.

A Phase 1, Open-Label, Dose Escalation Study of ASG-5ME in Patients with Pancreatic or Gastric Adenocarcinoma. Seattle Genetics. Closed to accrual.

A Randomized, Phase II, Multicenter, Double-Bline, Placebo-Controlled Study Evaluating The Efficacy and Saftey of Onartuzumab (MetMAb) in Combination with 5-Fluorouracil, Flinic Acid, and Oxaliplatin (mFOLFOX6) in Patients with Mestatatic HER2-Negative Gastro-esophageal Cancer. Genentech. Closed to Accrual.

Randomized, Double Blind, Phase II Study of FOLFOX Bevacizumab with MetMAb versus Placebo as First Line Treatment for Patients with Metastatic Colorectal Cancer. Genentech/Sarah Cannon. Closed to Accrual.

SWOG S0809: A Phase II Trial of Adjuvant Capecitabine/Gemcitabine Chemotherapy Followed by Concurrent Capecitabine and Radiotherapy in Extrahepatic Cholangiocarcinoma (EHCC). SWOG. Closed to Accrual.

A Multicenter Randomized Placebo-controlled Phase 2 Trial of Gemcitabine plus GDC-0449 (NSC 747691), a Hedgehog Pathway Inhibitor, in Patients with Metastatic Pancreatic Cancer (10052747). NCI/CTEP. Opened to accrual Sept 1, 2009. NCI/CTEP NCI#8418. Closed to accrual (ARRA funded)

A Randomized, Double Blind Placebo Controlled Phase 2 Study of FOLFOX plus or minus GDC-0449 in patients with advanced gastric and gastroesophageal junction (GEJ) carcinoma. NCI/CTEP NCI#8376. Closed to accrual.

A Multicenter Random Assignment Phase II Study of Irinotecan and Alvocidib (flavopiridol) versus Irinotecan Alone for Patients with p53 wild type Gastric Adenocarcinoma NCI/CTEP NCI#8060. Closed to accrual.

A Phase 2, Randomized, Double-blind, Placebo-controlled Study Evaluating the Safety and Efficacy of FOLFIRI in Combination With AMG 479 or AMG 655 Versus FOLFIRI for the Second-line Treatment of KRAS-mutant Metastatic Colorectal Carcinoma. Amgen. Closed to accrual.

TEACHING ACTIVITIES:

University of Chicago Medical Center, Chicago, Illinois. 2010-present

For the College (B.A., B.S.):

(a) Didactic

2011- Annual Lecture on Career Development Seminar for Summer Research Students

(b) Clinical

2011- Preceptor weekly for undergraduate students (1 student per year).

For Graduate Programs (Masters, Ph.D,):

(a) Didactic

2011- Graduate Course CANCER BIOLOGY I CABI 30800: HUMAN CANCER PRESENTATION AND MODELING: Annually one lecture on Colon Cancer
Graduate Course CANCER BIOLOGY III
Annually one lecture on Gastroesophageal Cancer

2011- Annual Lecture on Career Development Seminar for Summer Research Students

For Pritzker School of Medicine (M.D.):

(a) Didactic

2011- Career Development In Oncology presentation one lecture per inpatient rotation.
2011- Annual Lecture on Career Development Seminar for Summer Research Students
2014 Teaching Assistant for MEDC-30011: Epidemiology and Research Design

- Epidemiology and Research Design MEDC-30011 Medical Student (year 1) Course: Small group session Instructor.

(b) Clinical

2010- Daily inpatient rounding 4 weeks per year. 0-2 students per rotation.
2011- M1 Longitudinal Program Preceptor weekly (1-2 students).

For Graduate Medical Education (Residency and Clinical Fellowships):

(a) Didactic

2010- Discussant, Medical Oncology Fellows Journal Club, Grant Writing, Board Review.
2010- Annual Lecture to First Year Fellows on “Gastroesophageal”, “Cholangiocarcinoma”, and “Translational Medicine Basics”.
2012 Discussant, Internal Medicine Residents Clinical-Pathologic Correlates Conference
2015 “Meeting Highlights: Gastrointestinal Cancer.” ASCO Trainee & Early-Career Oncologist Lounge. ASCO 2015, Chicago IL.
2016- Annual Lectures to Surgical Residents and Fellows (General and Cardiothoracic) for Esophagogastric Cancer.

(b) Clinical

2010- Daily inpatient rounding 4 weeks per year ~2-4 residents/interns, 2 fellows per rotation.
2010- Supervision of fellows, residents in outpatient GI oncology clinic weekly (0-3 fellows)

University of Chicago Medical Center, Chicago, Illinois. 2006-2010:

- Medical Student Lecture Series
  - "Myelodysplasia", "Mesothelioma", "Hepatocellular Carcinoma".

UCLA Medical Center, Westwood, California. 2004-2006:

- Distinguished Teacher Award for UCLA Interns and Medical Students.
  - Teaching clinical medicine to Interns and Medical Students.

Wayne State University Medical School, Detroit, Michigan. 2000-2003:

- Tutor for individual and group sessions:
  - Anatomy, Histology, Biochemistry, Physiology, Neuroscience.

University of Waterloo, Waterloo, Ontario, Canada 1995-1999:

- Teacher Assistant in Science laboratories at University of Waterloo:
  - Cell Biology, Histology, Microbiology, 1997-1999

Lambton Kent District School Board, Sarnia, Ontario, Canada. 1997-1999:

- Summer School Teacher Assistant
  - Mathematics, Grades 9-12.

University of Chicago Research Trainees/Mentees:

Highschool Mentorship:

2012: IMSA (Igniting and Nurturing Creative, Ethical Scientific Minds that advance the human condition
Jiwon Kwak
Nitya Pariti
2018: Ocean Malka Chicago EYES on Cancer Summer Study

Undergraduate Mentorship

2011: Ciara Zagaja – Laboratory Fellowship June-August 2011.

Graduate School Mentorship

2015/16: Sravya Tumuluru - preparation for Graduate School at University of Chicago Medicine & Biological Sciences, as a technician in my laboratory
Tumuluru S, Xu D, Xu P, Henderson L, Catenacci DVT. Targeted therapies for targeted populations: MET inhibition for *MET* amplified gastroesophageal cancer. *In Preparation*
2019- Meizi Liu- "Clinical trial design using Bayesian methods" biostatistics student in the department of Public Health Science. Master's Dissertation Committee.

Medical Student Letters/Mentorship/Teaching

2009- : Mohamed El Dinali – clinical reference letter
John Wojcik - clinical reference letter
Obinna Orji – clinical reference letter

Longitudinal Program at Pritzker for MS1

2010-2011: Christine Anterasian
David Bluhm
2011-2012: Claire Naus
Alan Hutchison
2012-2013: Chenyu Lin
Arjun Dayal
2013-2014 Jennifer Jones (MS3)
Guarav Ajmani
Daniel Camacho
2014-2015 Chijioke "CJ" Ikonte

2015-2016 Chantai Tian

2011 University of Chicago Pritzker Summer Research Program – Cluster Group Leader

Resident Mentorship

2010: Anna Halpern – (yr 3) clinical reference letter, career development
2014: Andrew Hantel – (yr 1) translational research in GI malignancies
2017-2018 Syed Abdur-Rahman – clinical trial coordinator, internal medicine residency letter application
2019- Joseph Thomas – cholangiocarcinoma MSI-High tumors and response to immune checkpoint inhibitors.

Fellow Mentorship

2010: Manish Sharma - OSI-906 clinical LOI/protocol design and submission
2011: Ahad Sadiq - ARQ197 clinical LOI for GEC first line metastatic.
Dan Geynisman - ARQ197 clinical LOI/correlates papillary renal cancer, Cholangiocarcinoma
2012: Emilio Araujo Mino - clinical reference letter
Dan Geynisman - Upper Gi Maligancies
2013: Amikar Sehdev - Upper Gi Maligancies
Erica Ramsdale - Upper Gi Maligancies
Vassiliki Saloura - Upper Gi Maligancies
Andrea Amico - Family Risk of Upper and other GI Malignancies
2014: Andrea Amico - Family Risk of Upper and other GI Malignancies

- Amico A, Nielsen S, Geynisman D, Rambo B, Carey GB, Gulden C, Facekenthal J, Olopade O, **Catenacci D.** Challenges of applying tumor genome analysis to the germline: Examples from GI Oncology. AACR Cancer Susceptibility and Cancer Susceptibility Syndromes conference. San Diego, CA. January 29-February 1, 2014.

Hollis Walker - Upper and other GI Malignancies
Jen Veneris - Upper GI Malignancies
Steve Maron - GI database procurement/Colon cancer expression analysis mass spec
Chris Chapman - Upper GI malignancies, EUS portal venous sampling for CTCs and cfDNA

- Waxman I, Chapman C, Koons A, Konda V, Siddiqui U, Gelrud A, Xu P, **Catenacci DVT.** Detection of Portal Vein (PV) Circulating Tumor Cells (CTCs) in Pancreatic Cancer (PC) patients obtained by EUS guided PV Sampling. A safety and Feasibility trial. Accepted as an Oral Presentation. Digestive Disease Week 2014. Chicago, IL. May 4-6, 2014.

2015/16: Steve Maron -Immuno-Oncology Molecular Profiling of esophagogastric cancer
-GI database procurement/Brain metastases project

- Maron S, Luke J, Hovey R, Bao R, Gajweski T, Ji Y, Seiwert T, **Catenacci DVT.** Molecular Characterization of T-Cell-Inflammed Gastroesophageal Cancer. WIN 2016, Paris France. Best Abstract and Oral Presentation.

Hollis Walker - Upper and other GI Malignancies
Nanna Sulai - Upper and other GI Malignancies
Shuang Q Zhang - Pancreatic Cancer and other Upper and other GI Malignancies

- Zhang SQ, **Catenacci DVT**. How **c**an next-generation diagnostics aid pancreatic adenocarcinoma treatment? *Future Oncology* Mar 2016. 26831761

2016/17: Steve Maron -Immuno-Oncology Molecular Profiling of esophagogastric cancer
-GI database procurement/Brain metastases project

- Maron S, Luke J, Hovey R, Bao R, Gajweski T, Ji Y, **Catenacci DVT.** SITC annual conference, Orlando FL Feb, 2017. Identification of T cell-inflamed gastric adenocarcinoma in TCGA
- *Pectasides E, *Stachler MD, *Dersk S, *Lui Y, *Maron S, Islam M, Alpert L, Kwak H, Kindler HL, Polite BP, Sharma MR, Allen K, O'Day E, Lomnicki S, Maranto M, Kanteti R, Fitzpatrick C, Weber C, Setia N, Xiao SY, Hart J, Nagy RJ, Kim KM, Choi MG, Min BH, Nason KS, O'Keefe L, Watanabe M, Baba H, Lanman R, Agonston T, Oh DJ, Dunford A, Thorner AR, Ducar MD, Wollison BM, Coleman HA, Ji Y, Posner M, Roggin K, Turaga K, Chang P, Hogarth K, Siddiqui U, Gelrud A, Ha G, Freeman SS, Rhoades J, Reed S, Gydush G, Rotem D, Davison J, Imamura Y, Adalasteinsson,

Lee J, Bass AJ, **Catenacci DVT**. Genomic Heterogeneity as a Barrier to Precision Medicine in Gastroesophageal Adenocarcinoma. *Epub ahead of print Oct 4 Cancer Discovery 2017.* PMID 28978556 * co-first authors

Maron SB, **Catenacci DVT.** Novel Targeted Therapies for Esophagogastric Cancer. *Epub Surg Oncol Clin N Am* 2017. PMID: 28279470.

Maron SB, **Catenacci DVT.** Update on Gastroesophageal Adenocarcinoma Targeted Therapies. *Epub Hematol Oncol Clin North Am* 2017. PMID: 28501091

- Maron SB, Lomnicki S, Chase L, Joshi S, Nagy B, Lanman R, Lee J, Catenacci DVT**.** 'Genomic landscape of cell-free DNA in patients with gastroesophageal adenocarcinoma' *manuscript in preparation.*

Sope Olugbile - TCR sequencing in patients (MSI-H) receiving immunotherapies
Kevin Wood - Upper and other GI Malignancies
Smita Joshi - Merck LOI perioperative immunotherapy for gastroesophageal cancer

- Joshi SS, Maron SB, **Catenacci DVT**. Pembrolizumab for treatment of advanced gastric and gastroesophageal junction adenocarcinoma. Nov 2. doi: 10.2217/fon-2017-0436. [Epub ahead of print] 2017 *Future Oncology*. PMID: 29094609

2017/19: Smita Joshi – GI clinical oncology, clinical trials, translational GI research
Anu Neerukonda – GI clinical oncology

2018-20 Natalie Reizine – GI Oncology, Pharmacogenomics Program, UGT1A1 genotype directed dosing of irinotecan in GI malignancies.

- Clinical trial IIT: A Phase 1 Dose Titration Study of UGT1A1 genotype directed dosing of Irinotecan combined with 5FU, leucovorin, oxaliplatin and docetaxel in patients with advanced upper gastrointestinal adenocarcinoma

2020 Joseph Heng - Upper and other GI Malignancies
2021- Carolina Soto - Upper and other GI Malignancies

Catenacci Lab Castle Foundation Scholars and Mentorship

The Castle Foundation Award is a gift provided by the Castle Foundation with intention for the fostering and training of students in the research of gastroesophageal cancer and other gastrointestinal malignancies. The funding is to support research conducted, with my supervision and mentorship, with the participation of i) students who have completed their Undergraduate Degree with the intention of applying to various Graduate Schools in in the medical field (Medical School, Graduate School, Nursing School, Physician Assistant School) or ii) Fellows completing their Oncology Fellowship with intention to have a career in Academia. A recent gift of $1.475million over 5 years was given to this translational/laboratory research effort.

2013-2016: Les Henderson – career development --> Senior Cytogenetic Technologist, WI

- Henderson L, Peng Xu, Rambo B, Liao WL, J, Hembrough T, **Catenacci DVT**. *KRAS* gene amplification defines a distinct molecular subgroup of gastroesophageal adenocarcinoma that may benefit from combined anti-RAS/RAF/MEK/ERK and PIK3/PTEN/mTOR/AKT pathway inhibition. AACR KRAS Feb 21-24, 2014. Orlando FL (Abstr 55).

2013-14: Brittany Rambo Physician Assistant (see contributions in publication list above)
2015-16: Rachel Rendak Nurse Practioner (see contributions in publication list above)
2014-16: Emily O'Day Physician Assistant (see contributions in publication list above)
2016-18: Samantha Lomnicki Medical School (see contributions in publication list above)
2017-2019 Steve Maron Coggeshall Fellow/Castle Foundation Scholar → MSKCC 12/01/18
K12 2018 - "The impact of intra-patient tumor genomic heterogeneity on immune environment heterogeneity and immune checkpoint blockade resistance."
ASCO YIA 2018 "Intra-patient tumor immune environment heterogeneity and immune checkpoint blockade resistance."
AACR YIA 2018 "Intra-patient tumor heterogeneity and checkpoint blockade resistance."

- Maron S, Alpert L, Kwak HA, Lomnicki S, Chase L, Xu D, O'Day E, Nagy RJ, Lanman RB, Cecchi F, Hembrough T, Hart J, Xiao SY, Setia N, **Catenacci DVT.** Targeted therapies for targeted populations: anti-EGFR therapy for *EGFR* amplified gastroesophageal adenocarcinoma. *Epub*

*ahead of print Feb 15 Cancer Discovery 2018.*PMID 29449271

2017-2019 Leah Chase Medical School Candidate (see contributions in publication list above)
2019-21 Natalie Reizine Fellow – Pharacogenomics and Heme/Onc Fellowship
Development of UGT1A1 genotyping and dose finding study with irinotecan in advanced GI malignancies.
Anthony Serritella PGY7 – Predictive biomarkers of treatment outcome – FCG3R SNPs
Katherine Zhou MS-IV – Predictive biomarkers of immunotherapy outcome – PDL1 and TMB heterogeneity in tissue biopsies
Ryan Johnson – MS-I - Analysis of ctDNA NGS to evaluate molecular heterogeneity and implications on targeted therapy treatment outcomes
2020- Nicole Arndt, Stephanie Moya, Bryan Peterson
Koosha Paydary

Journal of Clinical Oncology Precision Oncology/ASCO Reviewer Mentorship Program:

2019-2020 Lorenzo Gerratana, Xuemei Ji, Andrea Napolitano, Prantesh Jain.

CATENACCI

EXHIBIT B

In re: Valsartan, Losartan, and Irbesartan Products Liability Litigation
Case No. 19-2875

DANIEL CATENACCI, M.D.
AMENDED LIST OF MATERIALS CONSIDERED

MATERIALS CONSIDERED	BATES NOS.
MDL PLEADINGS AND GENERAL DOCUMENTS	
Am. Master Medical Monitoring Complaint	N/A
Am. Master Personal Injury Complaint	N/A
Am. Master Economic Monitoring Complaint	N/A
2020.12.31 Plaintiff Disclosure of Cancer Types	N/A
2021.02.11 Letter from Lori G. Cohen to Judge Vanaskie	N/A
2021.02.11 Letter from Adam Slater Providing an Overview	N/A
EXPERT REPORTS (WITH EXHIBITS)	
2021.07.04 Report of Dr. Mahyar Etminan	N/A
2021.07.06 Report of Dr. Stephen Hecht	N/A
2021.07.06 Report of Dr. Stephen Lagana	N/A
2021.07.07 Report of Dr. David Madigan	N/A
2021.07.06 Report of Dr. Dipak Panigrahy	N/A
DEPOSITION TRANSCRIPTS (WITH EXHIBITS)	
04.08.2021 – Transcript of Raphael Nudelman deposition	N/A
REGULATORY GUIDANCES AND DOCUMENTS	
Publicly Available Documents	
2017.12.11 FDA Drug Safety Communication: No increase in risk of cancer with certain blood pressure drugs--Angiotensin Receptor Blockers (ARBs)	N/A
2018.05.07 EMA: EMA reviewing medicines containing valsartan from Zhejiang Huahai following detection of an impurity: some valsartan medicines being recalled across the EU.	N/A
2018.07.13 FDA Announces Voluntary Recall, FDA News Release	N/A
2018.07.17 Teva Issues Voluntary Recall	N/A
2018.07.18 Recalled US Valsartan Labels	N/A
2018.07.27 FDA Update, Analysis of N-nitrosodimethylamine (NDMA) Levels in Recalled Valsartan in the U.S.	
2018.08.30 FDA Statement on Ongoing Investigation into Valsartan Impurities	N/A
2018.10.11 FDA Posts Redeveloped Spectrometry	N/A
2018.10.16 FDA Posts Alternative Spectrometry for Detecting Impurities ("Combined Direct Injection N-nitrosodimethylamine (NDMA) and N-nitrosodiethylamine (NDEA) Impurity Assay by GC-MS")	N/A
2018.11.27 Teva Announces Voluntary Recall of All Amlodipine	N/A
2019.01.25 FDA Statement on the FDA's ongoing investigation into valsartan and ARB class impurities and the agency's steps to address the root causes of the safety issues.	N/A

MATERIALS CONSIDERED	BATES NOS.
2019.03.19 FDA provides update on its ongoing investigation into ARB drug products; reports on finding of a new nitrosamine impurity in certain lots of losartan and product recall.	N/A
2019.04.04 FDA Statement – Update on Recall	N/A
2019.04.15 Laboratory analysis of valsartan products	N/A
2019.05.02 Laboratory analysis of valsartan products	N/A
2019.06.13 Valisure Citizens Petition	N/A
2020.10.02 FDA Overview of Guidance for Industry	N/A
2020.12.04 - Laboratory analysis of valsartan products - FDA	N/A
FDA Updates and Press Announcements on Angiotensin II Receptor Blocker (ARB) Recalls (Valsartan, Losartan, and Irbesartan) *available at* https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-angiotensin-ii-receptor-blocker-arb-recalls-valsartan-losartan Last accessed July 31, 2021	N/A
FDA, GENERAL ADVICE: This letter is to inform applicants with an approved or pending application for an angiotensin II receptor blockers (ARB) drug product (DP) *available at* https://www.fda.gov/media/122643/download Last accessed July 17, 2021	N/A
COMPANY DOCUMENTS PRODUCED	
2018.07.06 Teva Health Hazard Assessment re Valsartan	TEVA-MDL2875-00274341
2018.07.06 Teva Health Hazard Assessment re Valsartan/HCTZ	TEVA-MDL2875-00274351
2018.07.10 Health Hazard Assessment of Amlodipine Valsartan	TEVA-MDL2875-00680243
2018.07.10 Health Hazard Assessment of Amlodipine Valsartan HCTZ	TEVA-MDL2875-00680244
2018.06.29 Teva Toxicological Assessment of NDMA impurity in valsartan by Dr. Nudelman	TEVA-MDL2875-00274358
ZHP root cause	TEVA-MDL2875-00783229
Mylan root cause	TEVA-MDL2875-00019995
2019.07.03 Teva Risk Assessment Report for Valsartan Huahai	TEVA-MDL2875-00693424

MATERIALS CONSIDERED	BATES NOS.
2019.07.03 Teva Risk Assessment Report for Valsartan Mylan	TEVA-MDL2875-00693422
2019.07.18 Teva Valsartan Analytical Drug Substance & Drug Product Testing Results	TEVA-MDL-0063060
2018.11.12 Tox Assessment for NDEA in Valsartan by Dr. Nudelman	TEVA-MDL-00953115
2019.03.13 Tox Assessment for NDMA and NDEA in Sartan Drugs in Parellel	TEVA- MDL2875-00773542
CBE-30 for ANDA 091519 – Valsartan/HCTZ w/ ZHP API	TEVA-MDL2875-00001886
CBE-30 for ANDA 090642 – Valsartan w/ ZHP API	TEVA-MDL2875-00013107
sANDA Approval by FDA for ANDA 091519	TEVA-MDL2875-00133642
sANDA Approval by FDA for ANDA 090642	TEVA-MDL2875-00354034
Valsartan sales	TEVA-MDL2875-00019951
Valsartan sales	TEVA-MDL2875-00019954
Email with test results	TEVA-MDL2875-00546489
Response to FDA Request for Information (RFI) for Valsartan (Jan 30, 2019)	TEVA-MDL2875-00546490
Testing result of NDMA in valsartan	TEVA-MDL2875-00546493
Balkanpharma Oupnitsa results for NOMA content in Valsartan API, manufactured by Zhejiang Huahai Co.,Ltd	TEVA-MDL2875-00546494
Balkanpharma Oupnitsa results for NOMA content in Valsartan API, manufactured by Zhejiang Huahai Co.,Ltd	TEVA-MDL2875-00546495

MATERIALS CONSIDERED	BATES NOS.
Miscellaneous Study Report	TEVA-MDL2875-00546496
Bafkanpharma Dupnitsa results for NOMA content in Valsartan tabfets and Valsartan/HCT tablets	TEVA-MDL2875-00546511
LITERATURE	
Abdel-Hamid, N. M., Nazmy, M. H., Abdel-Ghany, M. I. & Nazmy, W. H. Cytokines as important playmakers of experimental hepatocarcinogenesis confounded by diabetes. Ann Hepatol 11, 118-127 (2012)	N/A
Abou-Alfa GK, Macarulla T, Javle MM, et al: Ivosidenib in IDH1-mutant, chemotherapy-refractory cholangiocarcinoma (ClarIDHy): a multicentre, randomised, double-blind, placebo-controlled, phase 3 study. Lancet Oncol 21:796-807, 2020	N/A
Abou-Alfa GK, Sahai V, Hollebecque A, et al: Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: a multicentre, open-label, phase 2 study. Lancet Oncol 21:671-684, 2020	N/A
Adams KF, et al, Body size and renal cell cancer incidence in a large US cohort study, Am J Epidemiol. 2008 Aug;168(3):268-77. Epub 2008 Jun 12	N/A
Adams, carcinogenic agents in undiluted mainstream smoke and side stream smoke of different types of cigarettes. Carcinogenesis, 8(5):729–731	N/A
Adamson, R.H., et al., "Chemical Carcinogenesis Studies in Nonhuman Primates," *Laboratory of Chemical Pharmacology, NCI-NIH* (1983).	N/A
Adamson RH, Chabner BA. The Finding of N-Nitrosodimethylamine in Common Medicines. Oncologist. 2020 Jun;25(6):460-462. doi: 10.1634/theoncologist.2020-0142	N/A
Ahotupa, M., Bussacchini-Griot, V., Bereziat, J. C., Camus, A. M. & Bartsch, H. Rapid oxidative stress induced by N-nitrosamines. Biochem Biophys Res Commun 146, 1047-1054, doi:10.1016/0006-291x(87)90753-4 (1987)	N/A
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Yurgelun MB, Kulke MH, Fuchs CS, et al: Cancer Susceptibility Gene Mutations in Individuals With Colorectal Cancer. J Clin Oncol 35:1086-1095, 2017	N/A
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• Supplement	
Zhu, Y., et al, "Dietary N-nitroso compounds and risk of colorectal cancer: a case-control study in Newfoundland and Labrador and Ontario, Canada," British J. of Nutrition (2014)	N/A
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RECORDS OF BELLWETHER PLAINTIFFS	
Bonmon, Yolanda	
Plaintiff Fact Sheet	
Plaintiff Fact Sheet, 04/28/2021	YBonmon-PFS-000001 – 748
Deposition	
Bonmon, Yolanda – 2021.04.20 – Transcript	N/A
1 – 2021.04.16 Plaintiff Fact Sheet	N/A
2 – 2021.04.16 Signed Declaration of Plaintiff Fact Sheet	N/A
3 – Photograph of Valsartan Bottle	YBonmon-PPR-000319
4 - 2019.06.17 Amended Complaint - Master Personal Injury Complaint	N/A
5 – 2020.07.21 Bonmon Short Form Complaint	N/A
6 – Bonmon Medical Records from Charles K. Embry, MD	YBonmon-CEmbry-000001 – 88
7 – Bonmon Pharmacy Records from Apothecare Pharmacy	YBonmon-ApothPIII-000001 – 13
8 – Bonmon Medical Records from Bluegrass Women's Healthcare	YBonmon-BlueWHC-000001 – 55
9 – Bonmon Medical Records from Central Medical Associates	YBonmon-CMA-000035 – 89
10 – Bonmon Medical Record from UK Healthcare	YBonmon-PPR-000030
11 – Bonmon Medical Records from Central Medical Associates	YBonmon-CMA-000035 – 89
12 – Bonmon Medical Records from Central Medical Associates	YBonmon-CMA-000001 – 34
13 – Bonmon Medical Records from Hardin Memorial Hospital	YBonmon-HMH-MD-000019 – 480

MATERIALS CONSIDERED	BATES NOS.
14 – Bonmon Medical Records from Charles K. Embry, MD	YBonmon-CEmbry-000001 – 88
15 – 2021.04.16 Plaintiff Fact Sheet	N/A
16 – Bonmon executed authorization for New Hope Foster Agency	N/A
17 – Bonmon records from New Hope Foster Homes, Inc.	YBonmon-NHFAFC-HR-000001
18 – Bonmon Executed Tax Authorization	N/A
Medical Records	
Plaintiff Produced Records	YBonmon-PPR-000001 – 658
Apothecare Pharmacy III	YBonmon-ApothPIII-000001 – 13
Bluegrass Women's Healthcare	YBonmon-BlueWHC-000001 – 59
Central Medical Associates PLLC	YBonmon-CMA-000001 – 267
Embry Charles, MD	YBonmon-CEmbry-000001 – 88
Hardin Memorial Hospital	YBonmon-HMH-000001 – 521
Laboratory Corporations of America	YBonmon-LCA-000001 – 7
Lincoln Trail Diagnostics	YBonmon-LTD-000001 – 52
Norton Cancer Institute	YBonmon-NCI-000001 – 11
Norton Healthcare	YBonmon-NortonHealthcare-000001 – 559
UK Albert B. Chandler Hospital	YBonmon-UKABCH-000001 – 162
Walgreen Company	YBonmon-WC-000001 – 9
Briones, Joe	
Plaintiff Fact Sheet	
Plaintiff Fact Sheet, 02/02/2021	JBriones-PFS-000001 – 190
Medical Records	

MATERIALS CONSIDERED	BATES NOS.
Plaintiff Produced Records	JBriones-PPR-000001 – 441
Citizens Medical Center	JBriones-CMCen-000001 – 407
DeTar Hospital	JBriones-DeTarH-000001 – 436
Envision Pharmacies	JBriones-EnvisionP-000001 – 2
Gastroenterology of Victoria	JBriones-GVictoria-000001 – 7
HEB Pharmacy	JBriones-HEBPharm-000001 – 2
Minocha, Gulshan MD	JBriones-GKMinocha-000001 – 217
Regional Path Assocs	JBriones-RPA-000001 – 2
University of Texas MD Anderson	JBriones-UTMDACC-RD-000001 – 39
University of Texas MD Anderson Cancer Center	JBriones-UTMDACC-000001 – 8520
Dufrene, Lana	
Plaintiff Fact Sheet	
Plaintiff Fact Sheet, 02/10/2021	LDufrene-PFS-000001 – 186
Medical Records	
Plaintiff Produced Records	LDufrene-PPR-000001 – 178
Cardiovascular Institute of the South	LDufrene-CIS-000001 – 183
Lady of the Sea General Hospital	LDufrene-LSGH-000001 – 77
Leonard J. Chabet Medical Center	LDufrene-LJCMC-000001 – 2271
Ochsner Family Doctor Clinic	LDufrene-OFDC-000001 – 193
Racelands Pharmacy	LDufrene-RPE-000001 – 13

MATERIALS CONSIDERED	BATES NOS.
Walmart Pharmacy	LDufrene-WMS-000001 – 20
Garcia, Robert	
Plaintiff Fact Sheet	
Plaintiff Fact Sheet, 03/12/2021	RGarcia-PFS-000001 – 283
Medical Records	
Plaintiff Produced Records	RGarcia-PPR-000001 – 434
Baylor St. Lukes Medical Center	RGarcia-BStLMC-000001 – 831
CVS Pharmacy	RGarcia-CVS-000001 – 25
Express Scripts Inc.	RGarcia-ES-000001 – 12
HEB Pharmacy	RGarcia-HEBPharm-000001 – 25
Kelsey Pharmacy Berthelsen	RGarcia-KelseyP-000001 – 3
Kelsey Seybold Clinic	RGarcia-KSC-000001 – 2128
Texas Digestive Disease Consultants	RGarcia-TexasDDC-000001 – 42
Walgreen Company	RGarcia-WC-000001 – 79
Kennedy, Paulette	
Plaintiff Fact Sheet	
Plaintiff Fact Sheet, 06/21/2021	PKennedy-PFS-000001 – 470
Medical Records	
Plaintiff Produced Records	PKennedy-PPR-000001 – 590
Baylor Scott and White Medical Center	PKennedy-BS&WMC-000001 – 438
Dallas Cardiac Associates	PKennedy-DCA-000001 – 25
Dallas Nephrology	PKennedy-DallasNephA-000001 – 125

MATERIALS CONSIDERED	BATES NOS.
Kroger Pharmacy	PKennedy-KrogerPharm-000001 – 9
Lajara, Rosemarie, MD	PKennedy-RLajara-000001 – 10
Medical City Dallas	PKennedy-MCDH-000001 – 453
Northstar Diagnostic Imaging	PKennedy-NStarDI-000001 – 33
Solis Mammography	PKennedy-SolisM-000001 – 34
Southern Endocrinology and Diabetes Association	PKennedy-SEndo&DA-000001 – 33
Texas Breast Specialists	PKennedy-TBS-000001 – 168
Texas Colon and Rectal Surgeons	PKennedy-TC&RSurgeons-000001 – 128
Texas Oncology	PKennedy-TOncology-000001 – 385
Walgreen Company	PKennedy-WC-000001 – 91
Dawson, Nellie	
Plaintiff Fact Sheet	
2020.05.14 Plaintiff Fact Sheet	NDawson-PFS-000092-000180
Medical Records	
Plaintiff-Produced Medical Records	NDawson-PPR-000001-000179
3HC Home Health Hospice Healthcare	NDawson-3HCHH-H-HC-000001-000114
Jordan And Assocs Gastroenterology PA	NDawson-J&AG-000001-000068
Riverdale Family Medicine PA	NDawson-RFM-000001-000332
UNC Health Care System Path Dept	NDawson-UNCHCS-PD-000001-000001

MATERIALS CONSIDERED	BATES NOS.
UNC HealthCare System Rad Dept	NDawson-UNCHCS-RD-000001-000001
Kinkela, Silvano	
Plaintiff Fact Sheet	
Plaintiff Fact Sheet, 06/11/2021	SKinkela-PFS-00001 – 641
Medical Records	
Plaintiff Produced Records	SKinkela-PPR-00001 – 430
Aaron, Jay S., MD	SKinkela-JSAaron-00001 – 85
Advance Urology Centers of New York	SKinkela-AUCNY-00001 – 33
East Virginia ENT Specialists	SKinkela-EVEN&TS-00001 – 18
Lackawana County Dermatology Associates	SKinkela-LVDA-00001 – 19
Optum Rx	SKinkela-OptumRx-00001 – 138
Pulmonary And Critical Care Specialists	SKinkela-P&CCS-00001 – 56
Sentara Leigh Hospital	SKinkela-SentaraLH-00001 – 262
Sentara Surgery Specialists	SKinkela-SSS-00001 – 749
Urology Associates of the Poconos	SKinkela-UAP-00001 – 62
Virginia Oncology Associates	SKinkela-VOA-00001 – 93
Walgreen Company	SKinkela-WC-00001 – 24
Suits, James	
Plaintiff Fact Sheet	
Fifth Amended Plaintiff Fact Sheet, 02/03/21	JSuits-PFS-001131-1224
Medical Records	
Plaintiff-Produced Medical Records	JSuits-PPR-000001-001335

MATERIALS CONSIDERED	BATES NOS.
Aetna US Healthcare Legal Support Svcs	JSuits-AUSH-000001-000002
John Deere - NRS	JSuits-JohnDeere-HR-000001-000001
McCaysville Internal Medicine	JSuits-McCIM-000001-000251
Mutual of Omaha Insurance Company Claims Dept	JSuits-MOIC-000001-000003
Premier Surgical Assocs Cleveland	JSuits-PremierSAC-000001-000048
Tallent Drug Store	JSuits-TDS-000001-000036
Uhlik, Allen, MD	JSuits-AUhlik-000001-000383
Lee, Robert	
Plaintiff Fact Sheet	
2020.12.23 Plaintiff Fact Sheet	RLee-PFS-000001-000167
Medical Records	
Plaintiff-Produced Medical Records	RLee-PPR-000001-000958
Blue Cross Blue Shield of South Carolina	RLee-BCBSSC-000001-000092
Ctrs for Medicare and Medicaid Svcs Region 4	RLee-CMMS-R4-000001-000126
Death Certificate Proof Of Authority	RLee-DCPOA-000001-000002
Family Healthcare Clinton	RLee-FH-C-000001-000404
Greenville Health System Patient Accts	RLee-GHS-BD-000001-000027
Greenville Health System Med Recs Dept	RLee-GHS-MD-000001-001985
Greenville Memorial Hosp Rad Dept	RLee-GMH-RD-000001-000017
Greenville Memorial Hospital -Billing	RLee-GMH-BD-000001-000005
Ingles Markets, Inc.	RLee-InglesM-000001-000029
Walmart Pharmacy	RLee-WMS-000001-000027
Meeks, Ronald	
Plaintiff Fact Sheet	

MATERIALS CONSIDERED	BATES NOS.
2021.01.15 Plaintiff Fact Sheet	RMeeks-PFS-000001-000288
Medical Records	
Plaintiff-Produced Medical Records	RMeeks-PPR-000001-006576
Central Arkansas Veterans Healthcare System Med Recs Dept	RMeeks-CAVHS-MD-000001-000011
Central Arkansas Veterans Healthcare System Path Dept	RMeeks-CAVHS-PD-000001-000002
Death Certificate Proof Of Authority	RMeeks-DCPOA-000001-000005
East Jefferson Cardiovascular Specialists Inc Med Recs Dept	RMeeks-EJCS-MD-000001-000163
East Jefferson General Hosp Path Dept	RMeeks-EastJGH-PD-000001-000001
East Jefferson General Hosp Med Recs Dept	RMeeks-EJGH-000751-002405
East Jefferson General Hosp Patient Accts	RMeeks-EastJGH-BD-000001-000027
East Jefferson General Hosp Rad Dept	RMeeks-EastJGH-RD-000001-000001
East Jefferson Internal Medicine	RMeeks-EJIM-000001-000057
Med Plaza ENT Physicians	RMeeks-MPENTP-000001-000036
Nola Discount Pharmacy Pharmacy	RMeeks-NDP-000001-000027
Ochsner Med Ctr Release of Information	RMeeks-OchsnerMC-MD-000001-003194
Ochsner Med Ctr Patient Accts	RMeeks-OchsnerMC-BD-000001-000124
Ochsner Med Ctr Kenner Med Recs Dept	RMeeks-OMC-K-MD-000001-000797

MATERIALS CONSIDERED	BATES NOS.
Ochsner Med Ctr Kenner Patient Accts	RMeeks-OMC-K-BD-000001-000010
Ochsner Med Ctr Kenner Path Dept	RMeeks-OMC-K-PD-000001-000001
Ochsner Med Ctr Kenner Rad Dept	RMeeks-OMC-K-RD-000001-000001
Ochsner Medical Complex - NR Cert Ltr	RMeeks-OMComp-000001-000001
Smith Kenneth B MD	RMeeks-KBSmith-000001-000175
Southeast Louisiana Veterans HealthCare System Rad Dept	RMeeks-SLVHCS-RD-000001-000062
Southeast Louisiana Veterans Health Care System	RMeeks-SLVHCS-RD-000008-000009
Tulane Univ Hosp and Clinic Rad Dept	RMeeks-TUHC-RD-000001-000003
Tulane Univ Hosp and Clinic Med Recs Dept	RMeeks-TUHC-MD-000001-000001
Univ Med Ctr New Orleans Rad Dept	RMeeks-UMCNO-RD-000001-000002
Univ Med Ctr New Orleans Patient Accts	RMeeks-UMCNO-BD-000001-000009
Univ Med Ctr New Orleans Path Dept	RMeeks-UMCNO-PD-000001-000001
Univ Med Ctr New Orleans Med Recs Dept	RMeeks-UMCNO-MD-000001-000389
Weygandt, Robert	
Plaintiff Fact Sheet	
2020.04.07 Plaintiff Fact Sheet	RWeygandt-PFS-000267-000355
Medical Records	

MATERIALS CONSIDERED	BATES NOS.
Plaintiff-Produced Medical Records	RWeaygandt-PPR-001547-001817
Abrams Royal Pharmacy II Pharmacy	RWeygandt-ARPharmII-000001-000002
Advanced Imaging Center	RWeygandt-AImagingCe-000001-83
Aetna US Healthcare Legal Support Svcs	RWeygandt-AUSH-000001-000013
Baylor Regional Med Ctr at Plano Med Recs Dept	RWeygandt-BRMCP-MD-000001-000307
Baylor Regional Med Ctr at Plano Path Dept	RWeygandt-BRMCP-PD-000001-000001
Baylor Scott and White Health Rad Dept	RWeygandt-BSW-RD-000001-000002
Baylor Scott and White Health - NRS	RWeygandt-BSW-PD-000001-000001
Baylor Scott and White Health Med Recs Dept	RWeygandt-BSW-MD-000001-000002
Baylor Scott and White Health	RWeygandt-BSW-BD-000001-17
Baylor Surgicare at Plano Patient Accts	RWeygandt-BSPlano-BD-000001-000002
Baylor Surgicare at Plano - NR Radiology Cert	RWeygandt-BSPlano-RD-000001
Blue Cross Blue Shield of Texas Claims Dept	RWeygandt-BCBST-000001-000048
Carrell Clinic - Medical	RWeygandt-CarrellC-000001-000057
Clinical Path Labs Inc	RWeygandt-CPL-000001-000004

MATERIALS CONSIDERED	BATES NOS.
Colon And Rectal Assocs of Texas	RWeygandt-C&RAT-000001-000027
Death Certificate Proof Of Authority	RWeygandt-DCPOA-000001-000004
DFW Smiles	RWeygandt-DFWS-000001-000018
Endocrine Assocs of Dallas	RWeygandt-EAD-000001-000342
Express Scripts Inc Recs	RWeygandt-ES-000001-000021
Fleshman James Jr MD	RWeygandt-JFleshamnJr-000001-000219
Heart Hosp Baylor Plano Med Recs Dept	RWeygandt-HHBP-MD-000001-000657
Hollabaugh, Eric, MD - Medical	RWeygandt-EHollabaugh-000001-000008
Lab Corp of America Med Recs Dept	RWeygandt-LabCorpA-MD-000002-000009
Legacy Heart Ctr Med Recs Dept	RWeygandt-LHC-MD-000001-000001
Med Ctr of Plano Med Recs Dept	RWeygandt-MCPlano-MD-000001-000122
Med Ctr of Plano Rad Dept	RWeygandt-MCPlano-RD-000001-000001
Med Ctr of Plano Path Dept	RWeygandt-MCPlano-PD-000001-000002
Med Clinic of North Texas PA	RWeygandt-MCNT-000001-000093
North Central Surgical Ctr	RWeygandt-NCSC-000001-000250
North Point Lab	RWeygandt-NPL-000001-000001

MATERIALS CONSIDERED	BATES NOS.
Plano Dermatology Assocs	RWeygant-PDA-000001-000003
Quest Diagnostics Irving	RWeygandt-QD-Irving-000001-000002
Safeway Inc Corporate Pharmacy Dept	RWeygandt-Safeway-000001-000017
Texas Health Presbyterian Hosp Dallas Patient Accts	RWeygandt-THPHD-BD-000001-000009
Texas Health Presbyterian Hosp Dallas Path Dept	RWeygandt-THPHD-PD-000001-000001
Texas Health Presbyterian Hosp Dallas Rad Dept	RWeygandt-THPHD-RD-000001-000001
Texas Oncology Pharmacy Sammons	RWeygandt-TOPS-000001-000002
Texas Oncology Plano Prestonwood Med Recs Dept	RWeygandt-TO-PP-MD-000001-000391
TMI Sports Medicine and Orthopedic Surgery - NR Cert	RWeygandt-TMISMOS-000001-000001
Verity Cancer Center	RWeygandt-VCC-000001-56
VerityPET CT	RWeygandt-VPET-CT-000001-000065
Verity PET CT Rad Dept	RWeygandt-VPET-CT-RD-000001-000087
Walgreen Company	RWeygandt-WC-000001-000006
Deposition	
2021.04.13 Weygandt, Martha Transcript	
1 - Plaintiff's Fact Sheet	N/A
2 - Declaration	N/A
Composite 3 - Bankruptcy petition	N/A
3 - Motion for Setting and Request for Expedited Hearing on Motion to Use Cash Collateral	N/A
4 - Master Personal Injury Complaint	N/A
5 - First Amended Short Form Complaint	N/A

MATERIALS CONSIDERED	BATES NOS.
6 – Medical Records	N/A
7 - Death certificate	RWeygandt-DCPOA-000001
8 – Follow Up Examination	RWeygandt-PPR-000217-229
9 – Patient Tax / Insurance	RWeygandt-Safeway-0003-17
10 – Medical Records from Endocrine Associates of Dallas, P.A.	RWeygandt-EAD-000055-60
11 - Medical Records from W B Carrell Memorial Clinic	RWeygandt-CarrellC-000003-6
12 - Medical Records from Cardiology	RWeygandt-HHBP-MD-000431-433
13 - Medical Records from Endocrine Associates of Dallas, P.A.	RWeygandt-EAD-000074-78
14 – Medical Records Bates 1-16 with cover page	N/A
15 - Medical Records Bates 570-605	N/A
16 - Pharmacy Defendants' Exemplar Defendant Fact Sheet	N/A
POST-MARKETING PERIODIC SAFETY REPORTS	
ANDA 077530 Valsartan Tablets 40 mg, 80 mg, 160 mg, 320 mg	
Teva Pharmaceuticals, 01 April 2015 – 30 June 2015	N/A
Teva Pharmaceuticals, 04 January 2016 – 03 April 2016	N/A
Teva Pharmaceuticals, 04 April 2016 – 03 July 2016	N/A
Teva Pharmaceuticals, 04 July 2016 – 03 October 2016	N/A
Teva Pharmaceuticals, 04 October 2016 – 03 January 2017	N/A
Teva Pharmaceuticals, 01 January 2017 – 31 March 2017	N/A
Teva Pharmaceuticals, 01 April 2017 – 30 June 2017	N/A
Teva Pharmaceuticals, 01 July 2017 – 30 September 2017	N/A
Teva Pharmaceuticals, 01 October 2017 – 31 December 2017	N/A
Teva Pharmaceuticals, 01 January 2018 – 31 March 2018	N/A
Teva Pharmaceuticals, 01 April 2018 – 30 June 2018	N/A
Teva Pharmaceuticals, 01 July 2018 – 30 September 2018	N/A
Teva, 01 October 2017 – 31 December 2018	N/A
ANDA 090642 Valsartan Tablets 40 mg, 80 mg, 160 mg, 320 mg	
Watson Laboratories, 05 January 2015 – 04 April 2015	N/A
Watson Laboratories, 05 April 2015 – 04 July 2015	N/A
Watson Laboratories, 05 July 2015 – 04 October 2015	N/A
Watson Laboratories, 05 October 2015 – 04 January 2016	N/A
Watson Laboratories, 05 January 2016 – 04 April 2016	N/A
Watson Laboratories, 05 April 2016 – 04 July 2016	N/A
Watson Laboratories, 05 July 2016 – 04 October 2016	N/A

MATERIALS CONSIDERED	BATES NOS.
Teva Pharmaceuticals, 05 October 2016 – 04 January 2017	N/A
Teva Pharmaceuticals, 05 January 2017 – 04 April 2017	N/A
Teva Pharmaceuticals, 05 April 2017 – 04 July 2017	N/A
Teva Pharmaceuticals, 05 July 2017 – 04 October 2017	N/A
Teva, 01 January 2018 – 31 December 2018	N/A
ANDA 091235 Amlodipine and Valsartan Tablets 5/160 mg, 10/160 mg, 5/320 mg, 10/320 mg	
Teva Pharmaceuticals, 01 June 2015 – 31 August 2015	N/A
Teva Pharmaceuticals, 01 September 2015 – 30 November 2015	N/A
Teva Pharmaceuticals, 01 December 2015 – 29 February 2016	N/A
Teva Pharmaceuticals, 01 March 2016 – 31 May 2016	N/A
Teva Pharmaceuticals, 01 June 2016 – 31 August 2016	N/A
Teva Pharmaceuticals, 01 September 2016 – 30 November 2016	N/A
Teva Pharmaceuticals, 01 December 2016 – 28 February 2017	N/A
Teva Pharmaceuticals, 01 March 2017 – 31 May 2017	N/A
Teva Pharmaceuticals, 01 December 2017 – 28 February 2018	N/A
Teva, 01 March 2018 – 28 February 2019	N/A
ANDA 091519 Valsartan and Hydrochlorothiazide Tablets 80/12.5 mg, 160/12.5 mg, 160/25 mg, 320/12.5 mg, 320/25 mg	
Watson Laboratories, 21 March 2013 – 20 June 2013	N/A
Watson Laboratories, 21 June 2013 – 20 September 2013	N/A
Watson Laboratories, 21 September 2013 – 20 December 2013	N/A
Watson Laboratories, 21 December 2013 – 20 March 2014	N/A
Watson Laboratories, 21 March 2014 – 20 June 2014	N/A
Watson Laboratories, 21 June 2014 – 20 September 2014	N/A
Watson Laboratories, 21 September 2014 – 20 December 2014	N/A
Watson Laboratories, 21 December 2014 – 20 March 2015	N/A
Watson Laboratories, 21 March 2015 – 20 June 2015	N/A
Watson Laboratories, 21 June 2015 – 20 September 2015	N/A
Watson Laboratories, 21 September 2015 – 20 December 2015	N/A
Watson Laboratories, 21 December 2015 – 20 March 2016	N/A
Teva Pharmaceuticals, 21 March 2016 – 20 March 2017	N/A
Teva Pharmaceuticals, 21 March 2017 – 20 March 2018	N/A
ANDA 200435 Amlodipine, Valsartan and Hydrochlorothiazide Tablets 5/16012.5 mg, 10/160/12.5 mg, 5/160/25 mg, 10/160/25 mg, 10/320/25 mg	
Teva Pharmaceuticals, 01 December 2014 – 28 February 2015	N/A
Teva Pharmaceuticals, 01 March 2015 – 31 May 2015	N/A
Teva Pharmaceuticals, 01 June 2015 – 31 August 2015	N/A
Teva Pharmaceuticals, 01 September 2015 – 30 November 2015	N/A
Teva Pharmaceuticals, 01 December 2015 – 29 February 2016	N/A
Teva Pharmaceuticals, 01 September 2016 – 30 November 2016	N/A
Teva Pharmaceuticals, 01 September 2017 – 31 August 2018	N/A

MATERIALS CONSIDERED	BATES NOS.
MISCELLANEOUS	
All Plaintiff Diagnosis & Treatment Report	
All Plaintiff Diagnosis & Treatment Report (additional data)	
All materials cited or referenced in my expert report and attachments	N/A
This list includes items Plaintiffs' experts relied upon. By so doing, Defendants and this expert are not waiving any arguments or objections related to admissibility.	N/A

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EXHIBIT C

Below is my fee schedule:

1) $1500 retainer (not included towards review time)
2) $600/hour for review and discussion
3) $750/hour for written reports, deposition preparation, deposition, trial preparation
4) $7500/day for trial

CATENACCI

EXHIBIT D

PRIOR TESTIMONY OF DANIEL CATENACCI, M.D.

As of August 2, 2021

Trial

1. *Brown v. Sekon*, Baltimore, MD. Trial testimony given 11/19/18
2. *Allen v. St. Luke's*, Idaho.Trial testimony given 4/1/19
3. *Torres v. Summers*, Circuit Court of St. Louis City, State of Missouri, Case No. 1722-CC10764. Trial testimony given 5/15/19
4. *Karen Korszenobojn-Berger v. Andrew Berger,* Sup. Ct. of New York, Kings County, Case No. 508237/2016E. Trial testimony given 7/8/19.

Deposition

1. *Wilcoxon v Gastroenterology & Nutritional Services*. Deposition given 3/16/21.
2. *Perkins v. Trinity*. Deposition given 1/11/21.
3. *Holbrook and Frohlichstein v. Washington University Clinical Assoc., et al.,* Circuit Court of the State of Missouri, Case No. 1922-CC1091, Deposition given 10/14/20
4. *Overstreet v. Fronda*. Deposition given 10/14/20
5. *Young v. Makhdoom*. Deposition given 8/4/20
6. *Creech v. Carolina Radiology Consultants, P.A. and Jeffrey E. Jones, M.D.* Deposition given 8/20/19 and 2/24/20
7. *Gross v. BNSF*. Deposition given 10/22/19
8. *Lopez v. United States*. Deposition given 8/2/19
9. *Torres v. Summers*, Circuit Court of St. Louis City, State of Missouri, Case No. 1722-CC10764. Deposition given 2/25/19.
10. *Allen v. St. Luke's, et al.* Deposition given 1/14/19
11. *Teresa Brown v. Jatinder S. Sekhon, M.D.* Deposition given 5/11/18
12. *Larry Ames v. Donne Graessle D.O.*, Circuit Court of Jackson County, Missouri, Case No. 1516-cv-18185. Deposition given 6/7/17
13. *Lerner v. Kelly*. Deposition given 2/24/17
14. *Robert Adams v. Poirot & Macoupin Family*. Deposition given 1/25/17